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Abstracts

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NO-01. LEPTOMENINGEAL CARCINOMATOSIS AND CONCURRENT BACTERIAL MENINGITIS IN A PATIENT WITH ESOPHAGEAL ADENOCARCINOMA: A CASE REPORT

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Leptomeningeal carcinomatosis is a devastating complication of malignancy and is rarely seen in esophageal carcinoma. Herein we describe a patient who was found to have not only leptomeningeal carcinomatosis from esophageal adenocarcinoma but also concurrent *Pediococcus* bacterial meningitis. A sixty-six year old man with known esophageal adenocarcinoma, which was previously treated with 5-fluorouracil and cisplatin with concurrent radiation therapy followed by transhiatal esophagectomy, presented sixteen months after initial treatment with failure to thrive and headache for one month. Diagnostic testing of cerebrospinal fluid revealed adenocarcinoma by cytology and *Pediococcus species* by culture. *Pediococcus* causing meningitis is uncommon, previously having been described in only one case report in the English literature. The concurrent finding of both of these conditions in our patient is extremely unusual. It is unknown if the concurrent conditions of leptomeningeal carcinomatosis and *Pediococcus* meningitis are related or independent conditions. We postulate several possible mechanisms for the causation of this unusual presentation and review recent literature regarding the treatment of these conditions.

NO-02. KARNOFSKY PERFORMANCE STATUS IS A MORE RELIABLE INDICATOR OF PROGNOSIS IN PATIENTS WITH HIGH-GRADE GLIOMA WHEN ASSESSED POST-OPERATIVELY

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INTRODUCTION: High-grade gliomas (HGG) are associated with a poor prognosis even when subjected to aggressive multimodal therapy. Understanding prognostic indicators leads to better risk stratification and more individualized treatment strategies. The Karnofsky Performance Score (KPS) is derived from a scale developed for patients with systemic malignancies but frequently used in this population. Patients presenting with HGG may experience dramatic shifts in performance status between the time of presentation and the early postoperative period. We evaluated the relative reliability of preoperative and postoperative KPS in prediction of prognosis in this population. METHODS: We conducted a retrospective cohort study of 171 patients surgically treated for HGG at a single institution. KPS was recorded from the preoperative and postoperative neuro-oncology assessments or retrospectively calculated if absent. Variables associated with survival in a univariate logistical regression analysis ($p < 0.10$) were included in a forward selection multivariate regression model. Probability values with $p < 0.05$ were considered significant. RESULTS: Mean age at diagnosis was 55.0 ± 17.3 years. Mean preoperative and 2-4 week postoperative KPS scores were 67.3 ± 14.3 and 77.9 ± 13.2, respectively. Mean overall survival was 19.4 ± 20.6 months. Radiation therapy and temozolomide were each independently associated with prolonged survival, whereas old age was associated with decreased survival. After adjusting for these variables, a postoperative KPS score of 80 or higher was independently associated with prolonged survival ($p = 0.006$), whereas preoperative KPS score showed no correlation with survival ($p = 0.522$). Postoperative KPS scores of 80-100 were associated with prolonged median survival when compared to scores of 0-70 (479 vs. 210 days, $p = 0.002$). CONCLUSIONS: Postoperative KPS is a reliable prognostic indicator in patients with HGG and is more closely correlated with survival than preoperative KPS. The use of postoperative KPS in future outcomes analyses or clinical trials for HGG may offer more accurate interpretation of the benefits of other interventions.

NO-03. TYPE 2 DIABETES AND OBESITY ARE INDEPENDENTLY ASSOCIATED WITH POOR OUTCOMES IN PATIENTS WITH HIGH-GRADE GLIOMA

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INTRODUCTION: High-grade gliomas (HGG) are associated with a poor prognosis even when treated with aggressive multimodal therapy. Understanding prognostic indicators may lead to better risk stratification and may highlight future targets for therapeutic interventions. Type 2 diabetes mellitus (DM) and obesity are known risk factors for poor outcomes in patients with systemic malignancies but are not well-studied in the brain tumor population. We aim to demonstrate that type 2 DM and elevated body mass index (BMI) are independent risk factors in patients with HGG. METHODS: We conducted a retrospective cohort study of 171 patients surgically treated for HGG (WHO Grade III and IV) at a single institution. Preoperative medical histories were used to calculate BMI and provide records of preexisting DM. Variables associated with survival in a univariate analysis were included in the multivariate Cox model if $p<0.10$. Variables with probability values >0.05 were then removed from the multivariate model in a step-wise fashion. RESULTS: Mean age at diagnosis was 55.0 ± 17.3 years. Fifteen (8.8%) patients had a preoperative history of type 2 DM. Fifty-eight (35.8%) patients had a BMI < 25, 55(34.0%) a BMI 25-30, and 49(30.2%) a BMI > 30. Radiation therapy, temozolomide treatment, and higher postoperative KPS score were independently associated with prolonged survival, whereas old age was associated with decreased survival. After adjusting for these variables, both DM ($p = 0.001$) and increasing BMI ($p = 0.003$) were independently associated with decreased survival. Diabetics had a decreased median overall survival (312 vs. 470 days, $p = 0.003$) and PFS (106 vs. 166 days, $p = 0.04$) compared to nondiabetics. Higher BMI (<25, 25-30, and >30) was also associated with decreased median PFS: 195 vs. 165 vs. 143 days, respectively. CONCLUSION: Preexisting DM and elevated BMI are independent risk factors for poor outcomes in patients with HGG. These conditions should be used in risk stratification in this population and may suggest potential targets of future interventions.

NO-04. COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (CTCAE) V3 TO CTCAE V4: HOW WE SIMPLIFIED THE PROCESS OF CAPTURING ADVERSE EVENTS FOR OUR CLINICAL TRIAL PATIENTS

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CTCAE V4 has had many changes in terminology and format. As we transitioned from V3 to V4, we realized much of much of the terminology did not apply to our unique brain/spine patient population and that some of the terms overlapped. We know that when a study is monitored, all terms have to be exact (adverse events [AE] and medication indications must match). The idea was to create an easier, abbreviated version of CTCAE for our daily use that would still allow accurate and detailed capture and documentation of adverse events, thus preventing queries during the monitoring process. The first step was to do a side by side comparison of the two versions. An in-service was held to present this comparison to our Clinical Research staff for discussion and input. The next step was to review all of the updated terminology and decide which terms should be used. Lastly, a new pocket sized CTCAE was created and was shared at a subsequent in-service. Because our institution faced staffing issues, it became apparent that we needed to simplify some of our daily activities to allow us to work smarter, not harder. Creating this abbreviated version helped all of our team (research nurses and data coordinators) to work more efficiently.

NO-05. OUTCOME OF CONTINUATION OF BEVACIZUMAB FOR RECURRENT GLIOBLASTOMA

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OBJECTIVE: A retrospective evaluation of combination therapy (bevacizumab plus a cytotoxic chemotherapy) following disease progression and treatment with single agent bevacizumab in adults with recurrent glioblastoma (GBM) with the objective of determining progression free survival (PFS). BACKGROUND: There is no standard therapy for recurrent GBM after failure of bevacizumab. METHODS: 100 adults, ages 36-84 years (median 62), with recurrent GBM were treated. All patients had previously been treated with surgery, concurrent radiotherapy and temozolomide, post-radiotherapy temozolomide and single agent bevacizumab at either

first (60 patients; 60%) or second recurrence (40 patients; 40%). Patients were treated with bevacizumab, once every 2 weeks and carboplatin (75 patients; 75%), cyclophosphamide (15 patients; 15%) or BCNU (10 patients; 10%) [BEV +]. Neurological evaluation was performed every 2 weeks and neuroradiographic assessment every 2 months. RESULTS: A total of 316 treatment cycles (median 3) of BEV+ were administered, for which there were 74 Grade 3 adverse events (AEs) in 29 patients (29%) and 20 Grade 4 AEs in 10 patients (10%). Following two months of BEV + , 60 (60%) patients demonstrated progressive disease and discontinued therapy. No patient demonstrated a response, although 40 patients (40%) demonstrated neuroradiographic stable response. Survival in the entire cohort ranged from 1 - 12 months with a median of 4 months (95% confidence interval [CI]: 3.9, 4.1). Median and 6-month progression free survival at 6 months was 2.5 months (range 0.5-6 months; 95% CI: 2.3, 2.7) and 5%, respectively. CONCLUSIONS: Bevacizumab plus a cytotoxic chemotherapy demonstrated limited efficacy and emphasizes an unmet need in neuro-oncology in adults with recurrent bevacizumab-refractory GBM.

NO-06. TOOLS OF THE TRADE: NURSE PRACTITIONER ROLE IN BEVACIZUMAB RELATED TOXICITIES IN GLIOBLASTOMA PATIENTS

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Glioblastoma is a high grade glioma (grade IV), which carries a poor prognosis with a median survival of 15 months in newly diagnosed patients (deGroot et. al, 2010) and 3 to 9 months in patients with recurrent disease (Cohen, Shen, Keegan, & Pazdur, 2009). This tumor type has an aggressive behavior due to its vascular characteristics and its ability to secrete vascular endothelial growth factor (VEGF), which promotes angiogenesis. Although angiogenesis is a natural physiologic process, it is also required for tumor growth and results in endothelial cell proliferation and accelerated invasion of tumor cells into new vasculature (Buie, 2008; Chamberlain, 2010; deGroot, 2010). The use of bevacizumab has been evaluated in multiple cancer types, such as colorectal cancer, non-small cell lung cancer, renal cell cancer, and breast cancer. In May 2009, bevacizumab received accelerated FDA approval as monotherapy for patients with recurrent glioblastoma. With its use as targeted therapy, there are associated toxicities, which include gastrointestinal perforation, hypertension, cardiac events, proteinuria, and posterior reversible encephalopathy syndrome (PRES) (Higa & Abraham, 2009). Wound healing, hemorrhage, and thromboembolism are known toxicities that are inherent to patients with glioblastoma as well. Thus, it is important to carefully assess subjective and objective complaints given the multitude of toxicities this patient population may encounter due to their primary brain tumor, bevacizumab therapy, or both. As nurse practitioners, we have a unique perspective in caring for glioblastoma patients who are receiving bevacizumab because of our advanced assessment skills, rapport with patients and family members, and clinical experience. Therefore, we must utilize these tools to facilitate our role in patient education, prevention and early detection, monitoring, evaluation, symptom management, and ongoing follow-up regarding bevacizumab-related toxicities.

NO-07. HYDROXYUREA FOR RECURRENT SURGERY AND RADIATION REFRACTORY HIGH-GRADE MENINGIOMA: A RETROSPECTIVE CASE SERIES

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BACKGROUND: Hydroxyurea (HU), an orally administered chemotherapy, has become the *de facto* standard therapeutic agent in patients with surgically and radiation refractory meningiomas based on a limited literature. OBJECTIVES: A retrospective case series of 35 patients with recurrent WHO Grade 2 (n = 22) or 3 (n = 13) meningioma treated with HU following progression after surgery and radiotherapy was conducted with primary study objectives of overall response rate and median and progression free survival (PFS) at 6-months. METHODS: 35 patients (25 women, 10 men; median age 63 years, range 34-86) with recurrent meningioma were treated with HU (1000mg/m^2 orally divided twice per day with one cycle operationally defined as 1 month of daily HU). All patients progressed radiographically after prior therapy with surgery (35/35) and radiotherapy (35/35: external beam radiotherapy 35/35; stereotactic radiotherapy 35/35). No patient received prior chemotherapy or targeted therapy before instituting HU. RESULTS: Patients received 0.5-7 cycles (median 2.0) of HU with modest toxicity (28.5% with any grade and 8.5% with grade 3+ anemia or fatigue). There were no radiographic responses; 43% of patients had stable disease and 57% manifested progressive disease at first evaluation. The overall PFS was 3.0% at 6 months (median 2 months; 95% CI: 1.6, 2.4). The majority of patients (80%) following progression on HU were subsequently treated on an investigational trial. CONCLUSIONS: In this retrospective case series, HU was generally well tolerated and convenient but appeared to have very limited activity. This raises questions of what constitutes effective salvage therapy and indicates an unmet need for alternative treatments for recurrent high-grade meningiomas.

NO-08. DIFFUSE LEPTOMENINGEAL RELAPSE FOLLOWING GROSS TOTAL RESECTION IN A SPINAL CORD PILOCYTIC ASTROCYTOMA WITH OLIGODENDROGLIAL FEATURES AND 1P19Q DELETION

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Leptomeningeal dissemination (LMD) occurs in less than 10% of all cases of pilocytic astrocytoma (PA). Most of the metastasis occurs from the brain to the spinal cord. PA with oligodendroglioma (OD)-like features have been reported, but the association of 1p19q deletion is extremely rare, so the clinical significance and optimal therapeutic strategy for this tumor subset remains unknown. We report a novel case of a 15-year-old male with NF1 who presented with a one-month history of neck pain. Neuroimaging showed a localized lesion in the upper cervical spine from C3 to C6 with no intracranial involvement. A gross total resection (GTR) was performed, and the pathology was consistent with PA with some OD-like features. Fluorescent in situ hybridization analysis revealed an associated 1p19q deletion. Seven months later, surveillance scans revealed diffuse LMD along the spine with intracranial extension. This case raises some important clinical issues. Firstly, no defined prognostic markers and therapeutic strategy are known in these rare tumors. Observation is recommended in NF1 patients with PA undergoing a GTR. Adjuvant therapy in such tumors is not needed. Whether PA with OD-like features and 1p19q deletion after GTR would benefit from adjuvant radiation or chemotherapy with alkylating agents like temozolomide needs to be profiled. Secondly, prognosis and therapeutic strategy could be enhanced by testing for the BRAF mutation, which is also seen in PA and may control whether these tumors behave more like a PA or an OD. This case typifies the need to embark on identification of correlating histopathology and molecular markers for such rare tumors. This would help in deciding the need and type of adjuvant therapy required after GTR to prevent relapses.

NO-09. A RETROSPECTIVE STUDY OF PATIENTS WITH MELANOMA BRAIN METASTASES RECEIVING CONCURRENT WHOLE BRAIN RADIATION AND TEMOZOLOMIDE

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PURPOSE: Metastatic melanoma is the second most common cancer to metastasize to the brain. It is typically treated using stereotactic radiosurgery with or without whole brain radiation therapy. Recently, the alkylating agent temozolomide, which has demonstrated activity in patients with brain metastasis and primary tumors, has been used with concurrent whole brain radiation to delay brain metastasis recurrence, increase survival, and improve the quality of life of patients with brain metastases. Compared to whole brain radiation alone, the addition of temozolomide to whole brain radiation may provide an additional benefit to patients with melanoma brain metastases. METHODS: In this retrospective study, we reviewed the outcomes of 29 patients treated for melanoma brain metastases from 2005 to 2009 at the H. Lee Moffitt Cancer Center. These results were then narrowed via retrospective chart analysis to a cohort of patients with brain metastasis receiving concomitant temozolomide and whole brain radiation. RESULTS: Our study noted a median progression-free survival of 20.4 weeks and an overall survival of 44.4 weeks for patients with melanoma brain metastases, compared to a historical median of 16 weeks with whole brain radiation alone. DISCUSSION: Despite the retrospective nature of this study, it would be useful to further evaluate these interesting findings with a prospective trial utilizing this combined regimen.

NO-10. A PHASE II TRIAL OF EVEROLIMUS IN PATIENTS WITH RECURRENT GLIOBLASTOMA MULTIFORME

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Glioblastoma multiforme (GBM) is the most common primary adult brain tumor, with approximately 10,000 new cases each year and a mortality rate of over 90% within 2 years. The pathogenesis of GBM is linked to defects in several growth factor signaling pathways, including the phosphatidylinositol 3-kinase (PI3K)-Akt- mammalian target of rapamycin (mTOR) pathway involved in cell survival and proliferation. Everolimus is an mTOR inhibitor that has shown clinical benefit in other malignancies. This 2-arm study aimed to explore the biological effectiveness of 2 doses of everolimus measured by inhibition of S6 phosphokinase in GBM tumor cells and determine the efficacy and safety of daily everolimus in patients with recurrent GBM. In arm 1, patients received everolimus 0 (n = 6), 5 (n = 6), or 10 (n = 5) mg/day for 7 days or prior to surgical resection, followed with postsurgical everolimus 10 mg/day until disease progression or unacceptable toxicity. In arm 2 patients (n = 24) received everolimus 10 mg/day until unacceptable toxicity or disease progression. Treatment duration was measured in 4-week cycles. The study was terminated early because of low enrollment and disease progression; inhibition of S6 phosphokinase was not analyzed because of low numbers. There was neither complete remission nor partial remission for any patient. The majority of patients in arm 1 and 9 patients (37.5%) in arm 2 had a best response of stable disease, primarily at cycles 2 and 3. Overall for patients in arm 1, the median progression free survival was 14.9 weeks. In arm 2, median progression free survival was 4.1 weeks. Karnofsky performance scores did not change from baseline to study termination. Adverse events were experienced by 88% of patients, serious adverse events by 24%, and 15% of patients withdrew from the study because of drug-related adverse events. In conclusion, efficacy of everolimus in GBM was not demonstrated in this study.

NO-11. A PHASE I STUDY OF TEMOZOLOMIDE AND INTRATHECAL LIPOSOMAL CYTARABINE IN PATIENTS WITH NEOPLASTIC MENINGITIS

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INTRODUCTION: We tested the safety of the combination of intraventricular liposomal cytarabine (IVent LC) plus oral temozolomide (TMZ) in patients with neoplastic meningitis (NM). METHODS: Eleven patients were treated. The starting dose of IVent LC was 50 mg every 14 days; starting TMZ dose was 150 mg/M2 daily, every other week (QOW). Because of severe toxicity in the first 3 patients, the starting dose was changed to 25 mg IVent LC for the first two intrathecal doses, increasing to 37.5 mg and 50 mg in later doses, combined with TMZ at 100 mg/M2 daily QOW increasing to 150 mg/M2, in cohorts of 3. RESULTS: Eleven patients (7 women, 4 men) were accrued. Their cancers were: breast (5), lung (3), melanoma (2), primary CNS lymphoma (PCNSL) (1). Median age was 48 (range 31-59), median Karnofsky performance score was 90 (range 60-100), 10/11 had imaging and 10/11 had cerebrospinal fluid evidence of NM at diagnosis. Grade 3 or 4 toxicities were suffered by 9/11 patients, 6 with hematologic toxicity, and 5 with arachnoiditis. Best responses were: not evaluable in 5 (because of death, toxicity, or intercurrent illness), progressive disease in 4, no change in 1, and complete remission in 1 (PCNSL). Median progression free survival was 6 weeks (range 1-32 weeks), median overall survival was 9 weeks (range 1-140+ weeks). One patient with PCNSL cleared the CSF of tumor cells and has remained clear > 140 weeks after additional treatments. CONCLUSIONS: This study demonstrated that the combination of 50 mg IVent LC every 14 days combined with oral TMZ 150 mg/M2 daily QOW was excessively toxic. Lower dosing of each drug was better tolerated but still did not result in favorable outcomes except in one case of PCNSL. Any further investigations of this drug combination and schedule should start at doses no higher than the lowest ones noted above.

NO-12. CNS METASTASES FROM GYNECOLOGIC CANCERS: THE MAYO CLINIC ARIZONA EXPERIENCE FROM 2000-2010

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Improved therapies for treatment of systemic malignancies have extended patient survival, which has resulted in increased frequency of brain metastases from gynecologic malignancies. There is a dearth of data in the literature thus far regarding the true prevalence and incidence of these metastases as well as analysis of the optimal treatment for this specific patient population. The main goal was to determine the frequency of CNS metastases and survival in this patient population at Mayo Clinic Arizona. Following institutional review board approval, we performed a retrospective chart review of patients diagnosed with CNS metastases from gynecologic cancers from December 31, 1999 to December 31, 2009. Out of a total of 1443 patients with a diagnosed gynecologic cancer, we identified 14 patients who subsequently developed brain metastases over 10 years. Median time to development of brain metastasis was 38.4 months (95% confidence interval 15.0 - 84.9). Median time between brain metastasis and death was 3.0 months (95% confidence interval 1.9 to 7.0). Whole-brain radiation therapy was used to treat 11 of the 14 patients, of whom 3 had been initially treated with surgical resection followed by radiotherapy (RT). Two of the three patients who had resection followed by RT appear to have extended survival and are alive at the time of the results analysis. This is the largest case series in the literature reviewing brain metastases from gynecologic cancers. The time to death parallels that of brain metastases from other cancers. RT remains a significant part of the treatment for patients with brain metastases. If surgical resection is possible, resection followed by RT appears to be associated with improved survival. The development of novel targeted therapies and small molecule oral agents may hopefully have a role for metastatic ovarian cancer in the future.

NO-13. MGMT BIOCHEMICAL ACTIVITY IS ASSOCIATED WITH MYELOTOXICITY FOLLOWING THERAPY WITH TEMOZOLOMIDE

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Inclusion of the methylating agent temozolomide (TMZ) during radiation therapy and then continuing TMZ as a single agent after radiation has improved survival in patients with newly diagnosed glioblastoma (GBM). However, treatment with TMZ is accompanied by clinically significant myelosuppression in a minority of patients. Suppression of bone marrow function compromises the efficacy of TMZ therapy by necessitating dose reduction or discontinuance of treatment. A method to identify patients susceptible to TMZ-induced myelotoxicity would be clinically relevant. Our hypothesis is that TMZ-associated myelotoxicity is associated with low bone marrow levels of O^6-methylguanine-DNA methyltransferase (MGMT), the DNA repair machinery that removes cytotoxic O^6-methylguanine DNA adducts induced by TMZ and is reflected in human peripheral blood lymphocyte MGMT activity. To test our hypothesis, MGMT biochemical activity was assayed as well as determination of *MGMT* promoter CpG methylation status, a surrogate measure of MGMT gene expression. Three patient populations were studied: 8 glioma patients treated with TMZ showing no cytopenia; 10 glioma patients treated with TMZ showing clinically relevant myelotoxicity (Grade 3 or higher neutropenia, thrombocytopenia, or anemia); and 10 disease-free, untreated controls. Mean MGMT activity was 1.6-fold lower in TMZ-treated patients with myelotoxicity compared to treated patients with myelosuppression (9.9 ± 5.7 vs. 16.3 ± 8 fmol/10^6 cells; $P \leq 0.056$) and to disease-free, untreated controls (9.9 ± 5.7 vs. 15.7 ± 6.8 fmol/10^6 cells; $P \leq 0.084$). All samples (all 3 patient groups) displayed unmethylated promoters. These data suggest that myelotoxicity in TMZ-treated patients may reflect a reduced capacity to remove TMZ-induced O^6-methylguanine adducts and promoter CpG methylation status is not indicative of MGMT expression in peripheral blood lymphocytes.

NO-15. RECURSIVE PARTITIONING ANALYSIS OF PROGNOSTIC VARIABLES IN NEWLY DIAGNOSED ANAPLASTIC OLIGODENDROGLIAL TUMORS

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BACKGROUND: Anaplastic oligodendroglial tumors are rare. Treatment is variable and chemotherapy (CT) and/or radiotherapy (RT) are the most common initial strategies. Median survival varies widely, but it is unclear if this results from prognostic factors or is related to differences in therapy. 1p19q analysis is commonly performed, but it is unclear how to incorporate this and other clinical variables into clinical decision making and prognostication. METHODS: We conducted a retrospective study of 1013 patients treated with various strategies for newly diagnosed disease. Recursive partitioning analysis (RPA) was performed to generate independent prognostic classes among 587 patients with known 1p19q status who were treated initially with CT and/or RT. Variables included for survival classification were: age (continuous), history of prior low-grade glioma, 1p19q deletion status, histology, tumor location, gender, extent of resection, and performance status. Kaplan-Meier curves were plotted to verify classification and tested for significance by log-rank. RESULTS: RPA identified 5 prognostic groups based on hazard similarity: class 1 (age <60, 1p19q codeleted), class 2 ($<$age 43, not codeleted), class 3 (age 43-60, not codeleted, frontal lobe tumor or age $>$ 60, codeleted), class 4 (age 43-60, not codeleted, not frontal lobe tumor or age 60-69, not codeleted), and class 5 (age $\geq$70, not codeleted). Survival differences were highly significant ($p < 0.0001$) with medians ranging from 9.3 years (95% CI: 8.4-16.) for class 1 to 0.6 years (95% CI: 0.5-9.9) for class 5. CONCLUSIONS: Five distinct classification groups were defined using RPA modeling of prognostic factors typically obtained during routine management of anaplastic oligodendroglial tumors. Adoption into clinical care and prospective validation may improve therapy for subgroups of patients.

NO-16. 59 YEAR OLD MAN WITH MULTIPLE EXTRACRANIAL METASTASES FROM ANAPLASTIC MENINGIOMA

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INTRODUCTION: Meningiomas are common, accounting for 20% of all intracranial tumors. The majority are World Health Organization (WHO) grade I, which are typically slow growing, and resection is often curative. Atypical meningiomas (WHO II) are more likely to recur, but this is commonly adjacent to the site of the original disease. Multiple extracranial metastases are very rare. Here we describe a patient who developed multiple extracranial metastases. CASE REPORT: The patient was a 59-year-old man with a six-month history of headaches. Imaging studies revealed a right frontal extra-axial mass infiltrating the right frontal lobe. Computed tomography of the chest, abdomen, and pelvis were unremarkable. Embolization and resection of the mass was performed with pathology showing a WHO grade II/III atypical meningioma with a Ki-67 index of 8.9%. A year later, the patient's surveillance magnetic resonance imaging revealed a large tumor recurrence. The resected tumor showed a WHO grade III/III anaplastic meningioma with a Ki-67 index of 32%. The patient received radiation (200 cGy $\times$ 30). Four months later, the patient suffered a fracture of his left humerus, and x-rays were highly suggestive of a pathological fracture. Biopsy of the site was consistent with atypical epithelioid proliferation. Imaging of the chest, abdomen, and pelvis showed a large mass in the right gluteus maximus muscle and multiple lytic lesions in the ribs, sternum, lumbar vertebrae, and pelvis. Fine needle aspiration and core biopsy of the gluteal mass showed malignant spindle to epithelioid tumor morphologically identical to the patient's anaplastic meningioma. CONCLUSION: We present a rare case of extracranial metastases of an atypical meningioma that recurred with more invasive features following resection. The pattern of spread in our patient is also rare because the lungs and pleura are quoted in the literature to be the most common site of metastases followed by intra-abdominal organs.

NO-17. EFFICACY AND SAFETY OF TEMOZOLOMIDE ADDED TO RADIOTHERAPY FOR GLIOBLASTOMA IN THE ELDERLY

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BACKGROUND: Radiation therapy plus concomitant and adjuvant temozolomide (TMZ) is the standard therapy for the patients with glioblastoma up to 65-70 years of age. However, in elderly patients with glioblastoma, the use of TMZ has been controversial. Although this is partly because of the toxicity of TMZ in elderly patients, the extent of the side effects has not been well evaluated. To clarify beneficial and adverse effects caused by TMZ in elderly patients, we retrospectively analyzed glioblastoma patients treated with radiation therapy plus TMZ. METHODS: From January 2004 to June 2010, 120 patients with newly diagnosed glioblastoma were treated with radiation therapy and TMZ. We divided the patients into an elderly group (age of 65 or older) and non-elderly group (age of younger than 65), and the outcome and toxicity of the therapy were compared between these two groups. RESULTS: A total of 57 patients were classified into the elderly group. The median overall survival and median progression free survival in the elderly group were 15.2 months (95% confidence interval (CI): 13.1-18.3) and 8.7 months (95% CI: 6.0-11.7), respectively. In log rank analysis, overall survival was significantly shorter in the elderly group than in the non-elderly group ($p = .029$). RPA score and MGMT promoter methylation were prognostic factors for overall survival. Although incidence of overall common toxicity criteria grade 3/4 toxicity in the elderly group was similar to that in the non-elderly group; grade 4 adverse events during concomitant course were more frequent in the elderly group than in non-elderly group (23% versus 8%; $p = .034$). CONCLUSIONS: The addition of TMZ to radiotherapy showed a favorable outcome even in elderly patients with glioblastoma. However, it increased the risk of grade 4 adverse events during the concomitant course, which might shorten the survival of the elderly patients. Optimal use of TMZ to reduce toxicity, especially in concomitant course, should be further clarified.

NO-18. CLINICAL OUTCOME OF GBM LONG-TERM SURVIVORS

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BACKGROUND: An increasing number of patients with glioblastoma multiforme (GBM) are alive longer than three years after diagnosis (long-term survivors). Therefore, there is an urgent need for data about their clinical outcome and quality of life to optimize the medical management and function of patients. METHODS: In this cross sectional study, we studied 17 GBM patients surviving for longer than three years. The patients were treated at the outpatient clinic of the Medical University Hospital Vienna. We assessed patientś clinical outcome to get global information about the circumstances under which they live 36 months and longer after initial diagnosis of GBM. RESULTS: We assessed 9 female and 8 male GBM long-term survivors with a median age of 51 years (24-71). Fifteen of them lived together with their partner (and children) and 2 lived alone. The mean of the summary-score of the Neuro Cog-Fx, a computerized instrument for neurocognitive assessment of patients with neurological diseases, was 89 (ranging from 66 to 111), for which results from 61-79 are defined conspicuous, 80-89 borderline, and $\geq$ 90 normal. The global health score ranged from 17% to 100% with a mean of 70%. Drowsiness and fatigue were the most stated physical problems. The Independent Activities of Daily Living Score ranged from 0-8 points with a mean of 7 points, and Barthel Index ranged from 35 to 100 with a mean of 92 points. Six patients showed impairment in their manual dexterity and one patient in mobility. Three patients showed conspicuous depression scores, 2 had conspicuous anxiety results. Furthermore, future uncertainty was stated by 12 patients. CONCLUSION: GBM long-term survivors show moderate impairment in their cognitive functions and often suffer from physical problems. However, the majority of the GBM long-term survivors is able to manage the activities of daily living independently. Nevertheless, global health and future prospects remain poor.

NO-19. ASSOCIATION OF D-DIMER PLASMA LEVELS WITH MORTALITY RISK IN PATIENTS WITH HIGH-GRADE GLIOMA

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There is evidence for activation of the blood coagulation system in patients with high-grade glioma, which is associated with an increased risk to develop venous thromboembolism (VTE). Interestingly, a systemic activation of blood coagulation and procoagulant changes in the hemostatic system has been observed even in the absence of VTE and implicated in tumor progression and angiogenesis. Therefore, our aim was to investigate the prognostic value of D-dimer, which indicates global activation of hemostasis and fibrinolysis, for overall survival and mortality risk in patients with high-grade glioma. We have measured D-dimer levels with a D-Dimer latex

agglutination assay in 148 patients with a high-grade glioma (mainly glioblastoma multiforme, median age [25th-75th percentile]: 53 [39-64] years; 53 women and 95 men). These patients were included in the Vienna Cancer and Thrombosis Study (CATS), a prospective observational cohort study of patients with newly diagnosed cancer or with progressive disease after remission. They were followed over 2 years until occurrence of VTE and/or death. Kaplan-Meier and Cox-regression analyses were applied for statistical calculation. During a median follow-up time of 364 [202-731] days, 79 (53.4%) patients died and 24 (16.2%) developed VTE. At study inclusion, the median D-dimer level was 0.66 [0.34-1.33] μg/ml. The cumulative survival probability for patients with elevated D-dimer (defined as levels $>= 75^{th}$ percentile) compared to patients with non-elevated D-dimer (levels $< 75^{th}$ percentile) were 57% versus 59% after 1 year and 33% versus 43% after 2 years. The univariate hazard ratio of D-dimer (per double increase) for mortality was 1.2 ([95% confidence interval (CI): 1.1-1.3], $p = 0.005$) and 1.1 ([95% CI: 1.0-1.2], $P = 0.212$) in multivariable analysis after adjustment for age, sex, and VTE. In conclusion, high levels of D-dimer were associated with an increased mortality risk in patients with high-grade glioma. However, this association disappeared after adjustment during multivariable analysis.

NO-20. EXTRANEURAL METASTASIS OF A NONGERMINOMATOUS GERM CELL TUMOR OF THE CENTRAL NERVOUS SYSTEM IN A PEDIATRIC PATIENT WITH A VENTRICULOPERITONEAL SHUNT: A CASE REPORT AND REVIEW OF THE LITERATURE

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Brain tumors are the most common solid tumors in childhood and account for about 20% of all pediatric malignancies (13, 15). Central nervous system (CNS) germ cell tumors are rare. They make up approximately 3% of cancers diagnosed in children less than 15 years of age. The majority of CNS germ cell tumors occur in the pineal region (45%) or the suprasellar region (35%). Germ cell tumors are classified as either germinomas or non-germinomatous germ cell tumors (NGGCTs). NGGCTs comprise a heterogeneous group of histologies including embryonal carcinoma, which is a more aggressive entity. NGGCTs are less radiosensitive than germinomas, and their prognosis following standard radiotherapy alone has been poor, resulting in about a 20-45% overall five-year survival (5, 9). With the more recent introduction of chemotherapy including both platinum-based and oxazaphosporine regimens, the overall four-year progression free survival (PFS) is currently about 67% (14). Extraneural metastasis (ENM) is a rarity in central nervous system (CNS) tumors, with an incidence between 0.5% and 2.0% (12, 13, 16, 18). We describe the case of a 7-year-old Caucasian boy who presented with a mixed malignant germ cell tumor with predominant embryonal carcinoma component. The patient underwent right ventriculoperitoneal (VP) shunt placement for hydrocephalus at the time of diagnosis. He received multiagent chemotherapy followed by second-look surgery. In spite of an initial response to chemotherapy, the patient had metastatic progression of disease within the craniospinal axis. He received craniospinal radiation and high-dose chemotherapy. Although he had resolution of CNS disease, follow up off treatment revealed extra-abdominal metastases. This is a rare case to discuss abdominal metastasis of a CNS germ cell tumor in a patient with a ventriculoperitoneal shunt. The influence of VP shunt placement on treatment and management decisions will be presented.

NO-21. RESPONSE PATTERNS OF HIGH-GRADE GLIOMA PATIENTS TREATED WITH THE TGF-BETA2 INHIBITOR TRABEDERSEN IN A RANDOMIZED PHASE IIB STUDY

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INTRODUCTION: High-grade gliomas overexpress TGF-Beta2, a key player in malignant tumor progression. The antisense oligonucleotide trabedersen has been shown to reverse tumor-induced immunosuppression via inhibition of TGF-Beta2 synthesis. An increasing body of evidence from clinical trials indicates that response patterns of immunotherapeutics are clearly different from those seen with chemotherapeutics. METHODS: This retrospective analysis uses data from an active randomized, controlled Phase IIb study comparing 2 doses of convection-enhanced delivered trabedersen with standard chemotherapy (temozolomide or procarbazine, lomustine, and vincristine) in patients with recurrent/refractory anaplastic astrocytoma (AA, n = 39) or glioblastoma (GBM, n = 95). The 2 trabedersen dose groups were pooled for this analysis and compared to the chemotherapy group. Radiological response (magnetic resonance imaging) and survival data were reviewed. RESULTS: Results for AA patients were: tumor control, i.e. stable disease (SD), partial response (PR), or complete response (CR), was seen in a higher percentage of patients in the trabedersen group compared to patients in the chemotherapy group (18 of 27 [67%] vs. 7 of 12 patients [58%]). Likewise, the percentage of patients with overall response (PR or CR) was higher in trabedersen-treated patients (13 of 27 [48%]) compared to chemotherapy-treated patients (4 of 12 [33%]). The median time to stable disease was short in both treatment groups, whereas the median time to response was longer with trabedersen than with chemotherapy. Median overall survival (mOS) was markedly longer in trabedersen-treated patients when compared to chemotherapy-treated patients (details will be presented at the poster). CONCLUSIONS: Trabedersen's immune-modulatory mode of action results in response patterns distinctly different from those observed with cytotoxic agents. In trabedersen-treated patients, tumor responses (CR or PR) occur later than in chemotherapy-treated patients, sometimes after initial stable or transient progressive disease, but responses are very durable. Tumor control is achieved rapidly with trabedersen. The mOS after trabedersen treatment is favorable compared with standard chemotherapy.

NO-22. ALTERNATIVE DOSING MAY IMPROVE CLINICAL OUTCOME IN BEVACIZUMAB-RESISTANT GLIOBLASTOMA

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Bevacizumab (BEV) prolongs progression-free survival in recurrent glioblastoma patients; however, at subsequent progression, there is no effective salvage therapy. There is preclinical evidence to suggest continuous VEGF inhibition may promote glioma resistance, and restoration of some VEGF activity may limit glioma invasiveness, although the clinical impact of this approach is unknown. We present preliminary data on alternative BEV dosing (AD-BEV; 5 mg/kg IV q 3-4 weeks) alone or in combination with chemotherapy that was initiated in five patients who progressed on standard-dose BEV (SD-BEV; 10 mg/kg IV q2 weeks). Overall survival (OS) in these patients from dose adjustment (1st progression on BEV) was compared to 21 patients from MD Anderson enrolled in clinical trials of SD-BEV who transitioned to a non-BEV containing regimen at progression (CG1) and to published data in patients continued on a SD-BEV containing regimen after progression (Quant 2009; CG2). Two of 7 patients exhibited DWI changes coincident with clinical decline and FLAIR/T2 changes at SD-BEV failure, with subsequent DWI imaging improvement following initiation of AD-BEV. Median OS from SD-BEV failure in CG1 was 11.7 weeks (0.6 weeks - 71.7 weeks) and 17.6 weeks in glioblastoma patients in CG2 (Quant 2009, personal communication), whereas median OS for the AD-BEV cohort was 48.7 weeks (19.1 weeks - 105.6 weeks), with 5 of 7 patients currently alive at the time of writing. Median age was 44, 50, and 49 for each group, respectively. Median number of treatment regimens was 4 for all groups. Survival following BEV progression remains poor despite multiple treatment attempts. In this small case series, OS from the time of SD-BEV failure and the initiation of AD-BEV exceeds that of patients remaining on SD-BEV-containing regimens. Early dose adjustment may prolong OS and should be further investigated for the treatment of recurrent glioblastoma with BEV failure.

NO-23. COMBINATION OF HISTOLOGICAL GRADING AND IDH GENE STATUS CLASSIFIES HIGH GRADE GLIOMAS INTO 4 DISTINCT SUBTYPES: A STUDY OF 270 HIGH GRADE GLIOMAS

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A recent publication analyzed survival of patients with high-grade gliomas (HGGs) based on WHO grading and isocitrate dehydrogenase 1 (IDH1) gene status. Applying their strategies, we divided 270 HGGs (115 grade III gliomas [GIII] and 155 glioblastomas [GBM][142 primary GBM, 13 secondary GBM]) experienced at out institution into 4 subsets: GIII with IDH1 mutation (GIII IDH1mut), GIII IDH1 wild-type (wt), GBM IDH1mut, and GBM IDH1wt. As previously reported, overall survival was the highest in

GIII IDH1mut followed by GBM IDH1mut, GIII IDH1 wt, and GBM IDH1wt ($P < 0.05$; there was no significance between GBM IDH1mut and GIII IDH1wt). We additionally investigated clinical (age, sex, KPS, Ki67 labeling index [LI], and extent of resection) and molecular factors (MGMT methylation [M] and copy number changes of 1p, 7p, 9p, 10q and 19q) in these 4 subsets. As a result, compared to GIII IDH1wt, GIII IDH1mut carried frequent 1p19q codeletions (39%:10%, $P = 0.0011$) and MGMT M (91%:46%, $P < 0.0001$) and less frequent 7p gains (11%:33%, $P = 0.0045$). Compared to GIV IDH1wt, GIV IDH1mut showed frequent MGMT M (82%:44%, $P = 0.024$). Compared to GIV IDH1mut, GIII IDH1mut showed low Ki67LI (17.0%:28.0%, $P < 0.0001$) and less frequent 7p gain (11%:42%, $P = 0.041$). Compared to GIV IDH1wt, GIII IDH1wt presented low Ki67LI (23.7%:36.7%, $P < 0.0001$) and less frequent 10q loss (10%:40%, $P = 0.0003$). Therefore, as a new finding, we present that these 4 subtypes of HGGs carried distinct background. Notably, GIII IDH1wt was a distinct subset both from GIII IDH1mut and GIV IDH1wt in prognosis. These simplified 4 categories of HGGs can identify a subset of tumors with similar histological and molecular backgrounds and are useful to estimate patients' outcome.

NO-24. PHASE II STUDY: CARMUSTINE IMPLANT (GLIADEL WAFER) PLUS ADJUVANT AND CONCOMITANT TEMOZOLOMIDE IN COMBINATION WITH RADIOTHERAPY IN PRIMARY GLIOBLASTOMA PATIENTS

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Both gliadel wafers and temozolomide have been shown in independent studies to prolong survival of patients with recurrent malignant glioma following surgery and radiotherapy. The aim of study was to determine the safety and efficacy of the administration of systemic temozolomide with a prolonged continuous schedule in combination with locoregional treatment using gliadel as an adjunct treatment to surgery and radiotherapy in primitive glioblastoma patients. Following maximal tumor resection, up to eight wafers of gliadel were positioned in the surgical cavity. All patients underwent standard radiation therapy, and temozolomide was continuously administered at the dose of 75 mg/sqm BSA, for 6 months until disease progression or unacceptable adverse events. The primary end-point was 12 months progression free survival (PFS-12), and secondary end-points were median survival time (ST) and toxicities. To date, 35 patients have been included (25 men and 10 women), with ages between 27 and 70 years. Median follow-up was 13 months (range 1-24). One patient was lost to follow-up for withdrawal of consent. Overall, 17 patients have shown disease progression, and 6 have died. Median PFS is 12.5 months, and projected estimated ST reaches 23 months. Seven patients had to prematurely stop temozolomide treatment because of toxicities (one for liver toxicity, one for renal function toxicity, 5 for myelotoxicity mostly affecting platelets), and 3 because of early tumor progression. CD4+ lymphocytopenia developed in 22 out of 34 patients; despite this, only a few infections developed. This is the first prospective study confirming the feasibility of combining temozolomide with radiotherapy and gliadel in de novo glioblastoma after surgery, with promising efficacy results for PFS; the precise delineation of the risk-benefit ratio and side effects needs more prolonged follow-up in a higher number of patients.

NO-25. INTRACRANIAL ESTHESIONEUROBLASTOMA RESPONSIVE TO BEVACIZUMAB

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Esthesioneuroblastoma is a malignant neuroectodermal tumor originating from the olfactory neuroepithelium. One prior case report suggested that salvage therapy with temozolomide, an alkylating agent, plus sunitinib, a multiple tyrosine kinase inhibitor with anti-angiogenic properties, may be effective. Bevacizumab is a specific inhibitor of the vascular endothelial growth factor (VEGF) ligand, preventing its interaction with receptors on endothelial cells. We report a case of esthesioneuroblastoma with widespread intracranial dural spread that progressed on temozolomide plus sunitinib but responded dramatically to bevacizumab. The patient is a 45 year-old man with Kadish Stage C esthesioneuroblastoma with intracranial extension, treated initially in 5/05 with anterior craniofacial resection and intensity-modulated radiation therapy (IMRT) (6120 cGy). Submandibular recurrence was treated in 11/07 with radical neck resection and IMRT (6000 cGy) with cisplatin followed by cisplatin and etoposide. In 3/10, he developed increasing right lid ptosis. Magnetic resonance imaging (MRI) showed a new right orbital mass and extensive dural and leptomeningeal enhancement. He was treated with 4 cycles of temozolomide 75 mg/sq m/d plus sunitinib 25-37.5 mg/day each for 42 and56 days, respectively, which lead to disease stabilization. In 12/10 he developed left leg weakness. MRI showed an increase in size of the right orbital mass and increased nodular and cystic dural enhancement with perilesional edema. He was then treated with bevacizumab 5 mg/kg every 2 weeks. The patient's left leg weakness rapidly resolved and his right ptosis improved. MRI after 6 weeks of bevacizumab therapy showed interval reduction in dural contrast enhancement, tumor cyst sizes, and perilesional edema. He continues to receive bevacizumab with stable disease and function after 150 days of therapy. This patient experienced dramatic disease regression following 3 doses of bevacizumab. This is the first report of a tumor response in esthesioneuroblastoma from bevacizumab therapy. This case suggests that anti-angiogenic strategies may play a role in salvage therapy for this tumor.

NO-26. RECURRENCE OF ROSETTE-FORMING GLIONEURONAL TUMORS OF THE FOURTH VENTRICLE AFTER SURGICAL RESECTION

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INTRODUCTION: Rosette-forming glioneuronal tumors of the fourth ventricle (RGNT) are a recently described tumor entity. These tumors most commonly involve the 4th ventricular region. Forty-three cases have been reported to date with only 1 of 43 cases documenting recurrence. We present 4 additional cases of RGNT, 2 of which recurred after initial treatment. METHODS: The electronic medical records of four patients with RGNT were reviewed. RESULTS: Patient #1 is a 34-year-old woman with a RGNT in the inferior cerebellar vermis that was completely resected with no recurrence at 6 years. Patient #2 is a 45-year-old male with a RGNT of the tectal region, which gradually increased in size over 2 years, after which it was biopsied. The patient has remained clinically and radiographically stable for 1.5 years. Patient #3 is a 22-year-old woman with a RGNT of the inferior cerebellar vermis that was completely resected. The tumor recurred 3.5 years later in the fourth ventricular region. The patient has been clinically and radiographically stable for 1 year since repeat resection. Patient #4 is a 25-year-old man with a RGNT of the inferior cerebellar vermis that was initially treated with resection. Disseminated recurrence was discovered 9 years later with tumor in the pineal, intraventricular, and sacral regions. The ventricular disease was treated with stereotactic radiosurgery. Continued progression of non-enhancing intraventricular disease prompted treatment with 12 cycles of temozolomide and cis-retinoic acid. All regions of tumor have remained stable for 2 years after completion of chemotherapy. CONCLUSIONS: RGNT is a rare neoplasm with a typically benign behavior after surgical resection in the majority of reported cases. In contrast to the single previous report of tumor recurrence, we report 2 of 4 cases with late recurrence despite complete surgical resection, suggesting that the clinical behavior of these tumors may be more variable than previously reported.

NO-27. EFFICACY AND SAFETY OF MONOTHERAPY WITH BEVACIZUMAB IN JAPANESE PATIENTS WITH MALIGNANT GLIOMA AT FIRST OR SECOND RELAPSE

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INTRODUCTION: Glioblastoma (GBM) is the most common and aggressive malignant primary brain tumor. For recurrent malignant glioma, there are no standard therapies established, and the prognosis remains dismal. In phase II trials of bevacizumab (Bev) in patients with recurrent GBM, Bev alone or in combination with irinotecan has shown efficacy as measured by objective response rate (ORR) and 6-month progression free survival (PFS6). This open-label, phase II trial evaluated the efficacy and safety of Bev alone for Japanese patients with malignant glioma at first or second relapse. METHODS: All patients did not respond to radiotherapy and temozolomide previously. Patients received Bev 10 mg/kg every 2 weeks and were radiographically evaluated every 6 weeks until disease progression or discontinuation. The primary endpoint was PFS6 for GBM patients. The secondary endpoints included PFS, ORR, overall survival (OS), and safety for all patients. RESULTS: Thirty-one patients with recurrent malignant glioma (16 men and 15 women; median age, 54 years; 29 GBM and 2 WHO Grade III) were treated. For the GBM patients, 17 patients were first-relapse and 12 patients were second-relapse. For patients with GBM, the PFS6 was 33.9%, median PFS was 3.3 months, ORR was 27.6%, disease control rate was 79.3%, and median OS was 10.5 months. Six patients who were taking corticosteroids at baseline decreased corticosteroid dosage and two patients discontinued corticosteroids. The most common toxicities (all grade) were proteinurea (41.9%), hypertension (32.3%), and diarrhea (25.8%). Toxicities of grade $\geq$3 were 41.9%, and the most common of these was hypertension (9.7%). Intracranial hemorrhage was noted in one patient (grade 1). Toxicities led to Bev discontinuation in only two patients (intracranial hemorrhage and neutropenia). No new safety signals for Bev were detected in any patients, and Bev was well-tolerated. CONCLUSION: Bev demonstrated efficacy and acceptable toxicity for Japanese patients with recurrent malignant glioma.

NO-28. RESPONSE TO BEVACIZUMAB: A ROLE FOR ANTI-ANGIOGENIC THERAPY IN RECURRENT PILOCYTIC ASTROCYTOMA IN ADULTS?

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Pilocytic astrocytomas (PA) are highly vascular, circumscribed glial tumors that are associated with a good clinical outcome after maximum feasible surgery. Tumor recurrence, although rare, can be associated with a more aggressive biologic behavior that may require the use of chemotherapy or radiotherapy (RT) in addition to surgery. Vascular endothelial growth factor (VEGF) is important for endothelial proliferation and tumor angiogenesis in high-grade gliomas, but its role in PA is less understood. We report the case of a 39-year-old male who presented with a localized left cerebellar enhancing lesion with extension into the brain stem, which yielded a diagnosis of PA after gross total resection. Over the next 4 years, the patient had five local recurrences; the first three were addressed with surgical resection (with no change in histology) with RT administered after the second recurrence. The next recurrence failed to respond to temozolomide given on a 5/28 day schedule for 1 cycle. Given the aggressive growth of the tumor, bevacizumab was initiated at 10 mg/kg every two weeks. MRI scans after a month showed a radiological response with reduction in the size of both the enhancing and nonenhancing components of the tumor and associated improvement of clinical symptoms. Although higher VEGF expression has been anecdotally reported in newly diagnosed PA and not recurrent tumor, our patient's favorable response to bevacizumab suggests that a subset of recurrent PA may be driven by VEGF signaling. Further clinical investigation of anti-angiogenic therapies targeting VEGF for treatment of adult recurrent PA is warranted, including identification of the appropriate patients for this therapy.

NO-29. SALVAGE CHEMOTHERAPY BASED ON O^6-METHYLGUANINE-DNA METHYLTRANSFERASE(MGMT) EXPRESSION STATUS FOR RECURRENT MALIGNANT GLIOMAS: EXPERIENCE OF 45 CASES

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OBJECTIVE: Expression of O^6-methylguanine-DNA methyltransferase (MGMT) is related to the drug resistance of malignant gliomas. We analyzed the efficacy of salvage chemotherapy based on MGMT expression status in patients with recurrent malignant gliomas. METHODS: A total of 45 patients with recurrent malignant gliomas were analyzed. The various chemotherapy regimens were administered according to the expression status of MGMT. The patients with MGMT-positive tumors received various forms of chemotherapy including a regimen with no-alkylating agent, TMZ dosage density regimen, TMZ plus cisplatin regimen, TMZ or nitrosoureas with a non-alkylating agent (teniposide [VM-26], cisplatin [DDP], carboplatin [CBP], isophosphamide [IFO], or etoposide [VP16]). There was no restriction on chemotherapy regimen for patients with MGMT-negative or tumors with undetermined MGMT status. RESULTS: A total of 30 of 45 patients were assayed for MGMT status. We identified negative expression in 14 cases and positive expression in 16 cases. An overall response rate of 26.7% and a disease control rate of 73.3% were obtained. There were no significant differences in therapeutic effect for different tumor grades or different MGMT status ($P > 0.05$). The progression-free survival (PFS) rate at 6 months was 53.3% and the survival rates at 1, 2, and 3 years were 64.4%, 35.6%, and 20.0%, respectively. The median overall survival time (OS) was 21.2 months. There were also no significant differences between the MGMT-negative and MGMT-positive groups in the PFS rate at 6 months (57.1% vs 56.3%, $p > 0.05$) and the OS (18.4 vs 26.1 months, $p > 0.05$).CONCLUSIONS: Salvage chemotherapy based on MGMT expression status can enhance the overall response rate and the disease control rate for patients with recurrent malignant gliomas and can also prolong their survival time.

NO-30. CHEMOTHERAPY FOR MALIGNANT GLIOMA PATIENTS: A SINGLE INSTITUTION EXPERIENCE WITH 57 CASES

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BACKGROUND: Chemotherapy has been documented to benefit patients with malignant gliomas. However, most gliomas express O6-methylguanine-DNAmethyltransferase (MGMT), which is related to drug resistance in glioma patients. In this study, we analyzed 57 patients with malignant gliomas who received chemotherapy to assess whether chemotherapy based on MGMT expression could be beneficial to patients with MGMT-positive gliomas. METHODS: Fifty-seven patients who were pathologically diagnosed with glioma from August 2000 to January 2006 at Cancer Center of Sun Yat-sen University and received chemotherapy were reviewed. Their cancers included 3 cases of anaplastic oligodendroglioma (AO), 36 cases of anaplastic astrocytoma (AA), and 18 cases of glioblastoma multiforme (GBM). Response and survival time of the patients were evaluated. RESULTS: Thirty-five patients with MGMT positive tumors received chemotherapy regimens that generally consisted of no-alkylating agent, cisplatin plus TMZ, or a combination of TMZ or nitrosoureas with a no-alkylating agent (teniposide (VM-26), cisplatin (DDP), carboplatin(CBP), isophosphamide(IFO), etoposide(VP16)). Twenty-two patients with MGMT-negative tumors received chemotherapy regimens without restriction, i.e., either nitrosoureas or TMZ were used. Although objective response (OR) and overall response rate (RR) in the patients with MGMT-negative tumors (40.9% and 72.7%) were higher than that in the patients with MGMT-positive tumors (22.9% and 60.0%), there was no statistical significance between the two groups ($p > 0.05$). The progression-free survival (PFS) in MGMT-negative and MGMT-positive patients were 8.5 months (95% confidence interval [CI] 4.8-19.3) and 6.7 months (95% CI 3.7-9.3), respectively, and overall survival (OS) was 20.3 months (95% CI 14.3-[Missing value]) and 16.1 months (95% CI 11.1-26.2), respectively ($p > 0.05$). CONCLUSION: Our results indicate that personalized chemotherapy for glioma patients based on MGMT expression can give satisfactory results, especially in patients with MGMT-positive gliomas.

NO-31. DELTA T1 (DT1) METHOD AS A TOOL TO EVALUATE TUMOR PROGRESSION IN BRAIN CANCER PATIENTS

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INTRODUCTION: Evaluation of precontrast and postcontrast T1-weighted images is the primary approach to monitoring patients with brain tumors. The precontrast images are used to distinguish enhancing lesions from other sources of bright signal, such as subacute hemorrhage or protein-containing fluid, on the postcontrast images. However, in some cases additional enhancement observed on the postcontrast images, above and beyond the brightness observed on the precontrast images, can be quite subtle and thus difficult to detect by direct inspection. As a solution, we have developed an automatic method, the delta T1 (dT1) method, for selection of regions of interest (ROI) by creating difference maps between standardized precontrast and postcontrast T1-weighted images. The dT1 method described here is a fast, reliable, and objective method to detect

even subtly enhancing tumors free of blood products. METHODS: Calculation of dT1 maps is a simple 2-step process. First precontrast and postcontrast anatomic images are standardized using a linear piecewise interpolation method that standardizes the dynamic range of the image such that a particular tissue type falls under the same intensity range. Next, the standardized precontrast image is subtracted from the postcontrast image to output dT1 maps. Also, we qualitatively analyzed more than 80 dT1 maps with corresponding dynamic susceptibility contrast perfusion scans to estimate a threshold for automatically selecting enhancing regions of interest that are comprised of active (i.e., perfused) tumor. RESULTS: We calculated dT1 maps for patients and correlated dT1 results with time to progression (TTP) as observed on clinical scans. Overall, we report that dT1 maps can detect tumor progression a few months before becoming visible on conventional MRI images. CONCLUSIONS: We report use of a newly developed dT1 method for two main applications: clear delineation of tumor residual upon surgery and early detection of tumor recurrence.

NO-32. RESPONSE OF RECURRENT GLIOBLASTOMA TO TARCEVA IN PATIENTS WITH PTEN AND EGFRvIII CONSERVATION

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BACKGROUND: The epidermal growth factor receptor (EGFR) is commonly amplified, overexpressed, and mutated in glioblastoma (GBM). Efficacy of anti-EGFR treatments have shown to be associated with EGFR deletion mutant variant III (EGFRvIII) and expression of PTEN (Mellinghoffl K, NEJM 353; 19, Nov 2005). The GEINO group has conducted a phase II study to evaluate the efficacy of tarceva treatment in patients with relapsed GBM. METHODS: To date 14 patients have been treated. All the patients were PTEN (+++), EGFR (+++), and EGFRvIII (+++) by immunohistochemistry. We intended to treat 40 patients. If after 14 patients there was only one response the trial will be closed. We report the results response rate, survival, and toxicity for 14 patients. Eligibility criteria were histologically proven GBM, radiologic progression, >18 years old, Karnofsky performance score >50, and adequate bone marrow and organ function. There was no limit on the number of prior relapses. No enzyme-inducing antiepileptic drugs were allowed. The primary endpoints were response and progression-free survival at 6 months (PFS6). RESULTS: We have treated 14 patients with recurrent GBM (7 man/7 women) with 150 mg of tarceva daily. Median age was 55 years. Median KPS was 80 and median number of prior relapses was 2. One partial response and 3 instances of stable disease have been reported to date. One patient remains stable at 18 moths. PFS6 was 10%. Median PFS was 1.6 moths (0.96-2.3). Dose reduction was not necessary. The main treatment-related toxicity was dermatitis grade 1 in 11 patients and grade 2 in 3 patients. Any grade 3 toxicity was documented. Median survival was 5 months (confidence interval [CI]:0.2-9.8). Correlation IHC, FISH, and PCR will be reported. CONCLUSIONS: Treatment with 150 mg daily tarceva in GBM relapsed with PTEN (+++) and EGFRvlII (+++) by immunohistochemistry showed minimal efficacy with low toxicity.

NO-33. EFFECT OF SEQUENTIALLY PROGRAMMED MAGNETIC FIELD (SPMF) THERAPY IN THE TREATMENT OF PRIMARY MALIGNANT BRAIN TUMOURS

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INTRODUCTION: A study to demonstrate the efficacy of SPMF therapy on 123 terminally ill cancer patients was published in Journal of the Science of Healing Outcomes in 2008 and showed promising results that substantiated the effectiveness of this therapy. This article demonstrates the efficacy of this new therapeutic modality, in treatment of brain tumors without any side effects. METHODS: 50 terminally ill patients from the subgroup with primary malignant brain tumors were included for the study. 5 out of 50 were from the pediatric age group. All the patients had completed standard modalities of treatment such as surgery or radiation with or without chemotherapy and were on palliative care. SPMFs are non-thermal and non-ionizing electromagnetic fields and work by sensitizing the cancerous cells and normalizing the cell membrane potential to halt the process of cell proliferation, normalizing the aberrant electromagnetic field of centrioles and microtubules to halt mitosis, and activating p53 and restoring its function. The patients were exposed to SPMF therapy for 1 h daily for 28 consecutive days and were assessed using the Karnofsky performance scale (KPS), Functional Assessment of Cancer Therapy (FACT), and MRI. RESULTS: The statistical analysis revealed a significant correlation between SPMF therapy exposure and Karnofsky score improvement (paired t-test, p value < 0.0001). Long-term review of the patients showed 40% of the patients survived for more than two years, and there was progressive regression of the tumors seen in MRI. CONCLUSION: With a single exposure of SPMF therapy for 28 days, patients consistently showed significant improvement in KPS scores, considerable pain relief, and improvement in quality of life. These findings suggest that SPMF has the potential to be first line of management for primary malignant brain tumors in the future.

NO-34. PREDICTIVE VALUE OF MEAN APPARENT DIFFUSION COEFFICIENT VALUE FOR RESPONSIVENESS OF TEMOZOLOMIDE-REFRACTORY MALIGNANT GLIOMA TO BEVACIZUMAB

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We treated patients with recurrent glioblastoma (GBM) post-temozolomide (TMZ) with bevacizumab (BV), a potent anti-VEGF monoclonal antibody and assessed the predictive value of measuring apparent diffusion coefficient (ADC) for BV response. Nine patients with post-TMZ recurrent or progressive high-grade gliomas [7 GBMs and 2 anaplastic astrocytomas (AA)] were treated with BV monotherapy at 10mg/kg biweekly starting in August 2009. Five patients underwent RT plus concomitant TMZ at the initial therapy. The average patient age was 57 (22-78), and median Karnofsky performance scale (KPS) score was 70 (30-90). The median BV line number was 2 (2-5). Two cases had undergone additional stereotactic radiotherapy within 6 months prior to BV. The response was determined according to the Macdonald criteria. The first MRI after BV therapy was performed within 2 weeks. A mean ADC value (mADC) of gadolinium-enhanced tumor contours was calculated using the Picture Archiving and Communication System in Kyorin University Hospital. After the first BV cycle, early post-treatment MRI demonstrated a decrease of evaluable tumor volume in 8 of 9 cases (88.9%). Partial response was obtained in four cases (44.4%), and the other four cases remained stable. Among a total of 15 individual evaluable enhancing lesions, 11 tumors shrank, whereas four did not respond. mADC values were above 1,100 (10-6mm2/sec) in all of the responding tumors; conversely, mADC values in all nonresponding lesions scored below 1,100 ($p = 0.001$). mADC values decreased after the first BV treatment in all lesions except for 1 that did not respond. KPS improved immediately in four cases (44.4%). Median progression-free survival was 2.2 months. BV monotherapy is active for patients with TMZ-refractory recurrent gliomas and leads to rapid lesion shrinkage and symptom relief at a high rate. The tumor mADC value may be a useful marker for prediction of BV response and thus patient selection.

NO-35. BEVACIZUMAB CAN BE AN EFFECTIVE THERAPY FOR RADIATION NECROSIS IN CHILDREN

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We report weaning a 13 year old boy with radiation necrosis off steroids with good symptom control using bevacizumab. The boy was diagnosed to have radiation necrosis using a T1-weighted MRI of the brain with gadolinium enhancement and FLAIR technique a few weeks after he received radiation therapy with 5400 cGy in 27 fractions and a boost of 900 cGy over a total of 6 weeks for a progressively worsening tectal glioma. His symptoms, consisting of headaches, blurring of vision, poor depth perception, and loss of balance, were partially controlled on dexamethasone but worsened whenever a steroid wean was attempted. As a consequence of having to be on steroids for several weeks, he developed several side-effects including hypertension, increasing adiposity, and striae on his extremities. Therefore, he was treated with bevacizumab at 7.5 mg/kg every 2 weeks for 6 months. He was successfully weaned off his steroids within a week of his first dose of bevacizumab. By the sixth treatment, his neurological symptoms had almost completely resolved, with significant improvement on postcontrast MRI. He did not have any adverse reactions to the therapy and is doing well at follow-up a year later. Vascular Endothelial Growth Factor (VEGF) is known to increase capillary permeability and worsen edema in radiation necrosis. Bevacizumab is a monoclonal antibody against VEGF. Although there have been a few case series regarding the effectiveness of bevacizumab in the treatment of radiation necrosis in adults, we could find only one other such study for the pediatric population. Bevacizumab can be an effective therapy in the treatment of

radiation necrosis in children without the side-effects encountered with steroid therapy. Further study is warranted on the dosage, frequency, duration, and safety of treatment with bevacizumab for cerebral radiation necrosis in children.

NO-36. PHASE I / II ADAPTIVE RANDOMIZED TRIAL OF VORINOSTAT, ISOTRETINOIN, AND CARBOPLATIN IN ADULTS WITH RECURRENT GLIOBLASTOMA MULTIFORME - RESULTS OF THE PHASE I ARM

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BACKGROUND: Therapeutic strategies against malignant gliomas have focused on DNA-damaging agents, antiangiogenic strategies, and signal transduction pathways. However, epigenetic processes such as DNA methylation and histone acetylation constitute novel therapeutic targets against gliomas. Vorinostat, a histone deacetylase inhibitor (HDACi), has shown preliminary activity in adults with recurrent glioblastoma. Based on the preclinical rationale that HDACi can overcome resistance to isotretinoin and carboplatin, we hypothesized that combining these agents with vorinostat would improve outcome in malignant gliomas. We report the final results of the phase I study of combinations of these agents preceding a 3-arm adaptive randomized phase II study. METHODS: Adults with recurrent malignant glioma, KPS $\geq$ 60, normal organ function, and no prior exposure to HDACi or carboplatin were enrolled into three treatment arms: vorinostat + isotretinoin (Arm-1), carboplatin + isotretinoin (Arm-2), or vorinostat + isotretinoin + carboplatin (Arm-3). Dose escalation was by a 3 + 3 design declaring MTD at the highest dose causing DLT in $<2/6$ patients. RESULTS: Toxicities among 43 evaluable patients included: Arm1-neutropenia, thrombocytopenia, pulmonary embolism, elevated AST (DLT) and hypertriglyceridemia (DLT); Arm2-neutropenia, thrombocytopenia (DLT) and hypertriglyceridemia; and Arm3: thrombocytopenia (DLT) and hypokalemia (DLT). MTD were established for Arm-1 (vorinostat 400 mg/d, days 1-7 and 15-21, isotretinoin 100mg/m2/d x21d) and Arm-2 (carboplatin AUC5, isotretinoin 100mg/m2/d x21d); Arm-3 required dose de-escalation to level -3 (vorinostat 300 mg/d, days 1-7 and 15-21, isotretinoin 100mg/m2/d x21d, carboplatin AUC4) because of DLT (grade 3/4 thrombocytopenia) at dose level 2. Six patients achieved progression free survival at 6 months (1 in Arm-1, 2 in Arm-2 and 3 in Arm-3). CONCLUSIONS: Although the 2-drug combination MTDs were established, the 3-drug combination of vorinostat + isotretinoin + carboplatin had significant toxicities precluding further testing despite preliminary evidence of activity in these heavily pretreated patients. The trial has been modified, replacing carboplatin with dose-dense temozolomide, and restarted with a lead-in phase I to be followed by a multicenter Bayesian adaptive randomized phase II study.

NO-37. CENTRAL NERVOUS SYSTEM ANGIOSARCOMA : DIAGNOSIS AND TREATMENT

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Primary CNS angiosarcoma is an extremely rare malignancy with approximately 17 cases reported in the literature in the last 25 years. This tumor is characterized by a high rate of local recurrence and a short median survival time. Therapy has been limited to surgical resection with or without radiation therapy, because of the conventional wisdom that sarcomas are generally not sensitive to chemotherapy. We report two cases of primary CNS angiosarcoma in an attempt to develop a rational approach to diagnosis and treatment given the rarity of this entity. A 35-year-old woman presented with exophthalmos that progressed over six months. Imaging studies demonstrated a homogeneous mass of the left retro-orbital area with peripheral enhancement. An initial attempt at surgical resection was aborted because of severe bleeding, but a second procedure following tumor embolization was successful. The second patient was a 47-year-old man who presented with sudden visual loss in the left eye. Imaging studies revealed a heterogeneously enhancing left sphenoid wing mass extending into the sphenoid sinus. Surgical resection resulted in a near-gross total resection. In both cases, neuropathological examination demonstrated angiosarcoma. No other primary sites were identified, and these two cases were presumed to represent primary CNS angiosarcomas. The first patient is doing well without progression at ten-month follow-up after completing radiation therapy with concurrent bevacizumab. The second patient exhibits no residual disease one month post-surgery. The therapy plan calls for radiation therapy, temozolomide, and bevacizumab. The paucity of relevant studies of primary CNS angiosarcoma precludes definitive judgment concerning optimal therapy; however, the literature suggests that surgery with the goal of gross total resection remains the standard of care. There may be a rationale for the use of antiangiogenesis agents such as bevacizumab or other newer chemotherapeutic agents. Finally, postoperative radiation therapy may provide benefit, particularly when gross total resection is not possible.

NO-38. A RETROSPECTIVE ANALYSIS OF THE EFFICACY AND TOLERABILITY OF LACOSAMIDE IN PATIENTS WITH BRAIN TUMOR

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BACKGROUND: As many as 30% to 50% of brain tumor patients present with seizures, and many more remain at risk of developing seizures over the disease course. The management of seizures in these patients is complicated by tumor growth and the numerous adverse effects and drug interactions of traditional anti-epileptic drugs (AEDs), which are seen more frequently in patients with brain tumors than in the general epilepsy population. To the best of our knowledge, there have been no published studies looking at the efficacy and tolerability of lacosamide in controlling seizures in patients with brain tumors. AIM: To determine the efficacy and tolerability of lacosamide in patients with brain tumors. DESIGN: We performed a retrospective chart review of the medical records of all patients with a diagnosis of a primary brain tumor who were placed on lacosamide at 5 academic medical centers with tertiary brain tumor programs in the U.S. The main outcome measures were seizure frequency and toxicities. RESULTS: The majority of the patients had gliomas (95%). Fifty-five (79%) patients had partial seizures only, and 12 (17%) had generalized seizures. Most (74%) of the patients were started on lacosamide because of recurrent seizures. Forty-six patients (66%) reported a decrease in seizure frequency, and 21 (30%) reported stable seizures. Most of the patients (n = 54, 77%) placed on lacosamide did not report any toxicities. DISCUSSION: Of the newer AEDs, lacosamide has not been evaluated in a population of patients with brain tumors. Our retrospective analysis demonstrated that lacosamide was both effective and well tolerated as an add-on AED in patients with brain tumors. Lacosamide's novel mechanism of action will allow for concurrent use with other AEDs as documented by its efficacy across many different types of AEDs used in our population.

NO-39. INTRAOCULAR LYMPHOMA DEVELOPED AFTER SALVAGE CHEMOTHERAPY FOR RECURRENT PRIMARY CNS LYMPHOMA AND PROMISING THERAPY-A CASE REPORT

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Intraocular Lymphoma (IOL) is a subset of primary central nervous system lymphoma (PCNSL), a rare form of non-Hodgkin's B-cell lymphoma. The frequency of IOL has been rising in immunocompetent patients. We report the challenges of obtaining a diagnosis and the treatment of a female patient who has developed IOL after three cycles of salvage therapy with intravenous methotrexate for her recurrent PCNSL 5 years after the initial diagnosis of PCNSL. A 68-year-old woman was diagnosed with a large B-Cell central nervous system lymphoma in 2005 by brain tumor biopsy. She was in remission after 5 cycles of high-dose methotrexate for three years. The patient received two additional courses of methotrexate for recurrences 3 and 4 years after the initial diagnosis. Four and a half years after the PCNSL diagnosis, she developed vitritis and received high dose solumedrol with very slight improvement. CSF cytology was negative. A vitrectomy of her right eye was performed, and pathology showed CD-20 positive large B-cells. Immediately following the diagnosis of IOL, we started her on intravenous rituximab and oral temozolomide concomitant with intravitreal injection of rituximab. Eventually, the temozolomide was discontinued because of hematologic toxicities. The patient had a total of 4 intravenous rituximab and 8 intravitreal rituximab treatments in both eyes. Her repeated vitreous biopsy showed no malignant cells. Her visual acuity has no further deterioration. IOL should be suspected in patients who present with vision impairment and have a history of PCNSL. CSF study might be negative in most of the patients with isolated IOL or even with PCNSL. Vitreous biopsy or vitrectomy with corresponding pathology is still the gold standard

in the diagnosis of primary intraocular lymphoma. Intravitreal rituximab injection concomitant with systemic rituximab and temozolomide might be a promising therapy for IOL. Further study of more cases is warranted.

NO-40. OPTIC NEUROPATHY IN GLIOMA PATIENTS AFTER RECEIVING RADIOTHERAPY AND BEVACIZUMAB: RISK FACTORS AND RELATED QUALITY OF LIFE ISSUES

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Focal beam radiation in combination with temozolomide is the standard treatment for malignant gliomas as well as nonresectable, high-risk WHO grade II gliomas. Bevacizumab treatment at time of recurrence is stipulated to increase the patient's survival. However, optic nerve neuropathy is one of the serious complications of radiotherapy, and there are very few articles that discuss the relationships between bevacizumab and optic nerve neuropathy in the patients who develop bilateral optic nerve neuropathy during or after their treatment. The purpose of this study is to identify cases of bilateral optic nerve neuropathy in patients that received focal radiation and bevacizumab and to delineate possible risk factors and related quality of life issues. The data collection protocol is approved by Institutional Research Board at University of California, Irvine. Two patients with bilateral optic neuropathy after receiving focal beam radiation and bevacizumab were identified. Both patients were started on bevacizumab due to their tumor progression 2 months after completing radiation therapy, and the median time from the end of radiation to the onset of visual decline was 10.5 months. Case #1 is a 70-year-old Hispanic man with a nonresectable, bifrontal LGO who developed bilateral optic nerve neuropathy 7 months after starting on bevacizumab. Case #2 is an 82-year-old Asian man with the diagnosis of left frontal lobe GBM who developed bilateral optic nerve neuropathy 13 months after the initiation of bevacizumab. Their mean radiation dose to the optic chiasm was 49.64 Gy. Focal beam radiation, as well as bevacizumab, plays an important role in the treatment of gliomas. However, it is imperative for patients with the diagnosis of frontal tumors who were started on bevacizumab shortly after radiation to have routine follow-up with neuro-ophthalmologist consultation, home health safety evaluation, clinical social worker involvement, and periodical MRI of the orbits if their symptoms warrants.

NO-41. EVEROLIMUS TREATMENT OF SUBEPENDYMAL GIANT CELL ASTROCYTOMAS (SEGAs) ASSOCIATED WITH TUBEROUS SCLEROSIS COMPLEX (TSC): THE EXIST-1 TRIAL

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TSC is a genetic disorder caused by mutations in either the TSC1 (encoding hamartin) or TSC2 (encoding tuberin) genes. Hamartin and tuberin normally form a dimer that inhibits mammalian target of rapamycin (mTOR); mutation of either TSC1 or TSC2 results in constitutive mTOR activation. CNS manifestations of TSC include cortical tubers, SEGA, epilepsy, mental retardation, and autism. Everolimus, an mTOR inhibitor, has recently demonstrated efficacy in an open-label phase 1/2 study, significantly reducing SEGA volume and frequency of epileptic seizures (Krueger et al. NEJM 2010; 363:1801-11). Based on these results, everolimus was approved by the FDA in 2010 for patients with SEGA not suitable for surgical resection. A double-blind, randomized, placebo-controlled, multicenter phase 3 study (EXIST-1; NCT00789828) is underway to further evaluate everolimus in patients with SEGA associated with TSC. Eligible patients (target = 99), stratified by use of anti-epileptic drugs and randomized 2:1 to receive everolimus or placebo, received oral everolimus starting at 4.5 mg/m^2/d (titrated to a blood trough level of 5-15 ng/mL). Brain MRI was performed at 3, 6, and 12 months after initiation of study treatment and annually thereafter until SEGA progression. Patients completed a 24-hour video electroencephalogram at baseline and at 6 months (or end of treatment for discontinuing patients). Skin lesions were assessed using the Physician's Global Assessment of Clinical Condition tool every 3 months. Blood was collected for analysis of PK, hematology, blood chemistry, plasma angiogenic molecules, and gene mutation analysis for TSC1 and TSC2 at baseline. Patients experiencing SEGA progression were unblinded, placebo patients were offered open-label everolimus, and they were then followed using the most recent brain MRI scan as baseline and taking further brain MRI scans at 3, 6, and 12 months and annually thereafter. Open-label treatment continued until SEGA progression. Efficacy and safety outcomes are expected in mid-2011 and will be presented.

NO-42. A METANALYSIS OF ALTERNATIVE SCHEDULE OF TEMOZOLOMIDE (TMZ) IN RECURRENT MALIGNANT GLIOMA (MG)

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BACKGROUND: Prognosis of recurrent MG is poor. Historic data from phase II trials in patients failing RT +/− TMZ with traditional D1-5 TMZ reported 6 months progression free survival (6mPFS) between 15-20% and median overall survival (OS) of 6-7 months. Based on the favorable toxicity profile, alternative TMZ (metronomic, dose intense, and dose-dense) schedules are possible and may overcome MGMT mediated resistance and downregulate angiogenesis. METHODS: The criteria used to identify relevant studies through literature search were clinical trials of MG using TMZ schedules other than D1-5 Q 28d reporting 6mPFS. Ten studies were retrieved. Pooled estimates, based on published data of survival estimates, were obtained according to standard meta-analysis procedures. Sensitivity analyses were performed to examine whether outcomes were associated with previous treatment. RESULTS: 6mPFS for all studies was 30% (95% CI 26-34) and 27% (95% CI 22-31) for the 8 studies not including chemotherapy-naive patients. OS data was available from 8 studies yielding a 12 month OS of 37% (95% CI 32-42) and 41% (95% CI 38-47) in 6 studies that excluded chemotherapy-naïve patients. All studies reported that alternative TMZ schedules were well tolerated. CONCLUSIONS: Heterogeneity and lack of a control arm make the interpretation of these studies difficult. However, the magnitude of 6mPFS and OS outcomes were similar across trials, and there is a modest benefit associated with alternative schedules of TMZ.

NO-43. CLINICAL FEATURES AND PROGNOSTIC FACTORS OF PATIENTS WITH BRAIN METASTASIS FROM HEPATOCELLULAR CARCINOMA: IS EXTRACRANIAL METASTASIS ASSOCIATED WITH LONGER SURVIVAL?

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Brain metastasis (BM) from hepatocellular carcinoma (HCC) is extremely rare and is associated with poor prognosis. The aims of this study were to define the clinical course and prognostic determinants of patients with this disease. Using data obtained between January 1994 and December 2009, all the HCC patients with BM treated in Sun Yat-sen University Cancer Center were retrospectively reviewed for demographic, clinical, and therapeutic variables. Univariate and multivariate survival analysis were performed to identify potential prognostic factors. Forty-one patients were identified with BM from HCC, which makes the total BM incidence 0.47%. The median age at diagnosis of BM was 48.5 years. Thirty three patients (80.5%) were male, and 30 patients (73.2%) had hepatitis B. Intracranial hemorrhage occurred in 19 patients (46.3%). Thirty three patients (80.5%) developed extracranial metastasis. Of the 18 patients receiving aggressive treatment (43.9%), 6 patients underwent surgical resection, 10 patients received stereotactic radiosurgery, and 6 patients received whole-brain radiotherapy. The majority of patients died as a consequence of BM (56.1%). Median overall survival after diagnosis of BM was 3 months (95% confidence interval: 2.2-3.8 months). Patients with aggressive treatment had significantly longer survival than those treated with conservative treatment (4.5 vs 1.5 months, $P = 0.001$). There was a significant survival difference between patients in RPA I or II compared to those in RPA III (6 vs 1 months, $P < 0.0001$). Patients with extracranial metastasis before or with the diagnosis of BM had a longer survival than those without extracranial metastasis (3.5 vs 1 months, $P < 0.0001$). In multivariate analysis,

extracranial metastasis, RPA, and treatment modality statistically impacted overall survival ($P < 0.05$). The rare incidence and poor prognosis of patients with BM from HCC was confirmed in this study. However, the patients with good performance state would benefit from proper aggressive treatments. The clinical implication of extracranial metastasis in BM from HCC should be further assessed in larger studies.

NO-44. ENDOCRINOLOGICAL EVALUATION OF THE EFFICACY OF GAMMA KNIFE RADIOSURGERY FOR REMNANT TUMOR IN CAVERNOUS SINUS AFTER TRASNSSPHENOIDAL RESECTION OF GROWTH HORMONE SECRETING PITUITARY MACROADENOMA

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The object of this study is to determine long-term effect of gamma knife radiosurgery (GKS) for the treatment of remnant tumor in the cavernous sinus (CS) after transsphenoidal surgery (TSS) of growth hormone (GH)-secreting pituitary macroadenoma. Seventeen patients who failed to achieve biochemical remission after TSS were followed for a mean period of 70.2 months (range 17-180) after GKS. All patients underwent regular hormonal examination including serum GH, IGF-1, oral glucose tolerance test, and combined pituitary function test (CPFT). Magnetic resonance imaging was performed 1-year after GKS and then at subsequent 1.5-year intervals. All remnant tumors were confined in the CS and treated with hormone-suppressive medication, sandostatin LAR before or after GKS. There were 13 women and 4 men with a mean age of 41.8 years (range 27-62). Ten patients (58.8%) achieved hormonal remission with a mean time of 47 months (median 40, range 18-129) after GKS, and mean marginal radiation dose was 27.9 Gy (range 14-35). Mean tumor volume decreased from 5.15 ml (pre-GKS) to 3.55 ml (last follow-up) ($P = 0.000$). Actuarial rates of remission at 2, 4, and 6 years were 12.5 %, 40%, and 64%, respectively. Intergroup comparison between the remission and non-remission groups revealed that those who had a minimum hormonal follow-up period of 48 months showed significant difference in both serum level of GH ($P = 0.023$) and degree of decreased GH percentile ($P = 0.014$) at 12 months after GKS. A significant new pituitary hormone deficiency after GKS was found only in the gonadal axis ($P = 0.032$) based on last follow-up CPFT. Radiation necrosis was detected in 4 patients. GKS in remnant tumor restricted to the CS after maximal resection of tumor in the sellar and suprasellar area is effective, especially for minimizing newly developed post-GKS hypopituitarism. However, care should be taken to avoid radiation-induced adjacent lobe necrosis after GKS in the CS.

NO-45. *IDH* MUTATIONS AND THEIR ROLE IN PROGRESSION OF LOW GRADE GLIOMAS

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Somatic mutations in the gene encoding isocitrate dehydrogenase 1/2 (*IDH1/2)* are frequently found in secondary malignant gliomas and are of prognostic value. It is still unclear whether *IDH* mutation status changes during the progression from low-grade (LGG) to secondary high-grade gliomas (sHGG). Samples of patients with LGG (WHO grade II) and their later sHGG were investigated. *IDH1/2* mutation and *MGMT* promoter status were analyzed. The data were categorized according to demographic parameters, tumor-related factors, therapy-related factors, and patients' survival. Our population comprised 100 patients. Median follow-up was 9.6 years. We investigated 45 sample pairs of LGG and their later sHGG. *IDH* mutations were found in 36/45 LGG (80%) and matching sHGG without any changes in the mutation status. Patients with *IDH* mutations showed a significantly improved OS (9.3 vs. 3.8 years) but no superior PFS or time to malignant transformation. Secondly, samples of 72 patients with sHGG (30 AA and 42 sGBM) were analyzed. 53/72 (73.6%) patients harbored *IDH*1/2 mutations. The presence of *IDH* mutations after malignant transformation correlated with significantly improved PFS (2.2 vs. 1.0 years, $p = 0.003$) and OS (8.7 vs. 4.3 years, $p = 0.005$). Patients with *IDH* mutations and methylated *MGMT* promoter had the longest OS. Thirdly, 73 patients with LGG were analyzed. 45/73 patients (61.6%) developed sHGG. Except for extent of surgery and patients' age ($p = 0.001$), all investigated factors (tumor location, *IDH* mutation and *MGMT* promoter status, radiation after first surgery, histological subtype) failed to show a strong association with superior OS or PFS in the multivariate analysis. The *IDH* mutation status is stable during the progression of LGG to sHGG. *IDH* mutations are a good prognostic marker for sHGG according to PFS and OS, but are not of clinical prognostic relevance in the low-grade stage. Patients with LGG only benefit from *IDH* mutations after malignant transformation.

NO-46. RTOG 0525: A RANDOMIZED PHASE III TRIAL COMPARING STANDARD ADJUVANT TEMOZOLOMIDE (TMZ) WITH A DOSE-DENSE (DD) SCHEDULE IN NEWLY DIAGNOSED GLIOBLASTOMA (GBM)

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Radiotherapy with concomitant and adjuvant TMZ is the standard of care for newly diagnosed GBM. MGMT methylation status may be an important determinant of treatment response. This trial, conducted by the RTOG, EORTC, and NCCTG, determined if intensified TMZ improves survival (OS) or progression free survival (PFS) in all patients or specific to MGMT status. Eligibility criteria included age > 18 yrs, KPS ≥ 60, and existence of a tissue block with $> 1cm^2$ tumor for prospective MGMT and retrospective molecular analysis. Patients were randomized to Arm 1: standard TMZ (150-200 mg/m^2 x 5 d) or Arm 2: dd TMZ (75-100 mg/m^2 x 21 d) q 4 wks for 6-12 cycles. Symptom burden, quality of life (QOL), and neurocognition were prospectively and longitudinally assessed in a patient subset. 833 patients were randomized (1173 registered). Inadequate tissue ($n = 144$) was the most frequent reason for nonrandomization. No statistical difference was observed between Arms 1 and 2 for median OS (16.6, 14.9 mo, $p = 0.63$), median PFS (5.5, 6.7 mo, $p = 0.06$), or methylation status. MGMT methylation was associated with improved OS (21.2, 14 mo, $p < 0.0001$), PFS (8.7, 5.7 mo, $p < 0.0001$), and treatment response ($p = 0.012$). Cox modeling identified MGMT status and RPA class as significant predictors of OS; treatment arm and radiation technique (EORTC vs. RTOG) were not. There was increased grade ≥ 3 toxicity in Arm 2 (19%, 27%, $p = 0.008$), which was mostly lymphopenia and fatigue. This study did not demonstrate improved efficacy for dd TMZ for newly diagnosed GBM regardless of methylation status. However, it confirmed the prognostic significance of MGMT methylation in GBM, demonstrated the feasibility of tumor tissue collection, molecular stratification, and collection of patient outcomes in a large transatlantic intergroup trial, thereby establishing a viable clinical trial paradigm. Support: NCI U10 CA 21661 and U10 CA37422.

NO-47. RANDOMIZED PHASE II STUDY OF NEOADJUVANT BEVACIZUMAB AND IRINOTECAN VERSUS BEVACIZUMAB AND TEMOZOLOMIDE FOLLOWED BY CONCOMITANT CHEMORADIOTHERAPY IN NEWLY DIAGNOSED PRIMARY GLIOBLASTOMA MULTIFORME

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First-line temozolomide (T) and radiotherapy is standard in glioblastoma multiforme (GBM). In second-line therapy, the combination of bevacizumab (B) and irinotecan (I) produces impressive responses. We investigated the efficacy of BT and BI. Newly diagnosed GBM patients were randomized to neoadjuvant bevacizumab q2weeks and temozolomide using a 5/28 days regimen (BT-regimen) or bevacizumab q2weeks and irinotecan q2weeks (BI-regimen) for 8 weeks. All patients then received standard conformal radiotherapy (60 Gy/30 fractions) combined with the BT or BI regimen as described; however, in the BT arm, temozolomide was administered daily ad modum Stupp during radiotherapy. Following radiotherapy, adjuvant BT or BI was continued as described for the neoadjuvant regimen until 24 weeks. The primary endpoint was response at 8 weeks. Secondary endpoints included 6-months PFS, overall survival, and toxicity. Response was assessed every 8 weeks using MRI (WHO bidimensional measurements) and McDonald criteria. Toxicity was assessed with CTCAE 3.0. All MRI were subsequently reviewed by an expert neuroradiologist who was blinded to treatment. 63 patients were included. The median age, performance status (0/1/2), and sex (male/female) in the BI/BT arms were 59/62, (20/10/1)/(13/17/2), and (18/13)/(21/11), respectively. Responses at 8 weeks in the BI/BT arms were: complete response 0/0, partial response 6/10,

minor response (25-50% reduction compared to baseline) 7/11, no change 7/6, and progressive disease 6/4. Five patients on the BI-regimen and one on the BT-regimen were non-evaluable at 8 weeks: 4 had non-enhancing tumors at baseline, and 2 had poor quality MRI at 8 weeks. All 6 were clinically nonprogressive and continued planned therapy. Hematological toxicity was more frequent with BT than BI, whereas the frequency of grade III/IV non-hematological toxicity was similar. There was 1 toxic death on the BT regimen. Response at 8 weeks seemed to favor the BT regimen and seemed to support current investigations of adding bevacizumab to Stupp's regimen in first-line therapy. Updated secondary endpoints will be available by November 2011

NO-48. SAFETY AND ACTIVITY OF INTRA-CSF TRASTUZUMAB IN PATIENTS WITH NEOPLASTIC MENINGITIS FROM BREAST CANCER OR PRIMARY BRAIN TUMORS

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OBJECTIVE: To establish the safety and activity of intra-CSF trastuzumab in patients with neoplastic meningitis from breast cancer or malignant primary brain tumors. BACKGROUND: Neoplastic meningitis is a devastating complication of extra-CNS malignancies and primary brain tumors with few available treatments. Trastuzumab, a large-molecule monoclonal antibody directed against the HER2/neu receptor (overexpressed on some breast cancers, glioblastomas, and medulloblastomas) has negligible access to the CSF after intravenous administration. Intra-CSF administration could circumvent this barrier. METHODS: Seven patients with neoplastic meningitis (4 GBM, 2 breast cancer, 1 medulloblastoma) and progressive neurologic deterioration were treated with intra-CSF trastuzumab (20-60 mg per dose, either weekly or every other week) for four treatments. Age ranged from 29 to 68 (median 53) years; KPS ranged from 70 to 90 (median 80). Patients who were neurologically stable or improved after four treatments were continued on therapy every other week until neurologic progression. CSF cytology, neurologic status, and KPS were assessed at each treatment. HER2/neu status of the primary tumors was also evaluated. RESULTS: One of the 2 patients with breast cancer (both HER2/neu+) and one of 4 GBM patients are responding clinically and cytologically 4 and 14 weeks after initiating treatment. The patient with medulloblastoma (also HER2/neu+) continues to respond clinically and cytologically after 5 weeks. Seven of 11 patients with GBM have responded (2 cytologically, all 7 clinically) with response durations ranging from 9 to 12+ weeks. HER2/neu status is being assessed. There were no adverse events related to the trastuzumab. CONCLUSIONS/RELEVANCE: Trastuzumab can safely be administered into the CSF in patients with solid tumor neoplastic meningitis. Sustained clinical and cytologic responses may occur in patients with breast cancer and primary brain tumors. HER2/neu status may predict response. Further study to establish the biologically optimum dose and efficacy of this agent may be warranted.

NO-49. USING-ADC/CBV RATIO AS A POTENTIAL IMAGING BIOMARKER TO CHARACTERIZE RESIDUAL/RECURRENT METASTATIC TUMOR FOLLOWING RADIATION THERAPY

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We sought to explore the use of a ratio between ADC values and maximum relative cerebral blood volume as a potential biomarker to diagnose residual or recurrent metastatic tumor from radiation necrosis following radiation therapy. In this retrospective study, we included 8 patients who were treated with radiation therapy for metastatic brain tumor and underwent conventional diffusion-weighted, diffusion-tensor MR imaging, and T2*-weighted dynamic susceptibility contrast MR imaging. Primary malignancies included breast, renal cell, lung, and testicular carcinoma. 3 patients developed increase in the size of the enhancing lesion on follow-up imaging, which is concerning for radiation necrosis or residual or recurrent tumors. 5 patients were found to have stability or decrease in the size of enhancing lesions on follow-up. The follow-up period ranged between 3-32 months. Regions of interest were drawn within the contrast-enhancing regions for ADC analysis. To derive maximum relative cerebral blood volume of the enhancing lesion, color maps were used to guide placement of ROIs in the lesion. This was normalized to normal-appearing white matter. The 3 patients with increased enhancement on follow-up imaging were found to have residual or recurrent tumor at surgery. The 5 patients with stable or decreased enhancement were assumed to be successfully treated. There appeared to be a negative correlation between ADC and rCBV max for all patients. For patients assumed to be successfully treated, the ADC/CBVmax ratio was essentially double the value of those associated with residual or recurrent tumor. Our preliminary work suggests that an ADC/rCBV max ratio may have utility to diagnose residual or recurrent tumor. Although no cases of pathologically confirmed radiation necrosis were found in those with increase in the size of enhancement, there appeared to be a potential difference between confirmed residual or recurrent tumor cases and those that appeared to be successfully treated. We feel that further study utilizing these metrics in a larger study population is warranted.

NO-50. COMPARING THE EFFECT OF NOVOTTF TO BEVACIZUMAB IN RECURRENT GBM: A POST-HOC SUB-ANALYSIS OF THE PHASE III TRIAL DATA

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BACKGROUND: NovoTTF-100A (Novocure Ltd.) is a portable device that uses disposable scalp electrodes to deliver low intensity, alternating electric fields that interfere with cell division. The device has recently been approved by the FDA for the treatment of recurrent GBM based on data from a phase III study in recurrent GBM. Bevacizumab (Avastin) is FDA-approved based on non-controlled data for the treatment of the same condition. This presentation will describe a post-hoc subanalysis of the phase III data comparing the outcome of patients randomized to receive either NovoTTF or bevacizumab in the ITT population. METHODS: 237 adults with recurrent GBM were enrolled in 28 centers in the US and Europe and assigned to receive either NovoTTF-100A (TTF, n = 120) administered continuously or the best available chemotherapy at the physicians discretion (BAC, n = 117). Of the 117 BAC patients, 36 had received bevacizumab alone or in combination with a cytotoxic chemotherapy. Patient characteristics in both TTF and bevacizumab groups were well balanced for age, KPS, recurrence number and prior surgical resections. Baseline tumor size was slightly smaller in TTF patients (14.5 vs. 15.3 cm^2). Twenty-three TTF patients (19.1%) and four BAC patients (11.1%) had failed bevacizumab prior to enrollment. Overall survival (OS) served as the primary endpoint, and PFS6 and 1-year survival were used as secondary endpoints. RESULTS: Overall survival in the ITT population was higher in TTF than bevacizumab patients (median 6.6m vs. 5.0m, respectively; p = 0.054; HR = 0.65). A Cox proportional hazards model showed this difference to be statistically significant (p = 0.048; HR = 0.65; 95%CI 0.51-0.90). 1-year survival in TTF patients was 22% vs. 14% in bevacizumab patients. PFS6 was 21% in both groups. CONCLUSIONS: This post-hoc analysis suggests a superior OS in TTF patients compared to patients who received bevacizumab. A randomized clinical trial should be performed to confirm the validity of this observation.

NO-51. O6-METHYLGUANINE-DNA METHYLTRANSFERASE ACTIVITY IS INVERSELY ASSOCIATED WITH PROGRESSION-FREE SURVIVAL FOLLOWING ALKYLATING AGENT THERAPY IN GLIOBLASTOMA AND ANAPLASTIC GLIOMAS

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Methylation of promoter CpGs in the O6-methylguanine-DNA methyltransferase (MGMT) gene is associated with better outcome following alkylator chemotherapy in glioblastoma (GBM) and anaplastic glioma (AG). Promoter methylation is indicative of suppressed gene expression, suggesting that low MGMT biochemical activity promotes alkylator sensitivity, a hypothesis yet to be unequivocally demonstrated in glioma tissue. Nonetheless, separation of GBMs into methylated and unmethylated categories and presumed alkylator sensitivity is imperfect in the clinic (50% of methylated GBM cases show alkylator resistance and 15% of unmethylated GBM cases show sensitivity). To address these shortcomings, we examined the correlation of MGMT activity in 77 de novo GBMs with progression-free survival (PFS) following alkylator therapy and promoter methylation status determined by methylation-specific PCR (MSP). Cox regression analysis revealed a significantly greater risk for early progression (HR = 2.06, CI = [1.26; 3.36], $P \leq 0.004$) for GBM with MGMT activity greater than the median (i.e., 5.2 fmol/106 cells; ~3,100 molecules/cell). This association was observed for tumors treated with concurrent temozolomide and radiation or with alkylators given after radiotherapy. MSP analysis of 44 of the GBMs revealed 10 tumors (23%) with methylated promoters. Tumors with less than median MGMT activity were more likely to display methylated promoters (41% vs. 11%; $P \leq 0.02$). In addition, mean activity was 3-fold lower in methylated GBMs than in unmethylated tumors (14

vs. 4.7 fmol/106 cells; $P \leq 0.0001$). Comparable associations between MGMT activity and PFS or promoter methylation status were also observed for 72 AG. These results provide direct evidence in GBM and AG that MGMT activity promotes resistance to alkylating agents in vivo and that promoter methylation is indicative of low MGMT activity. However, there is considerable overlap of MGMT activity between methylated and unmethylated tumors, suggesting that this activity may be used to identify GBMs that do not respond to alkylator therapy as predicted by methylation status.

NO-52. FET-PET POSITIVE BRAIN LESIONS: A COMPARISON OF ^{18}F-FET-PET, MRI, AND HISTOPATHOLOGICAL FINDINGS

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BACKGROUND: Because of the high incorporation rate of the labeled amino-acid ^{18}F-fluoroethyl-L-tyrosine (^{18}F-FET) into glioma cells ^{18}F-FET-PET is increasingly used for diagnosis, treatment planning, and monitoring of gliomas. The specificity of ^{18}F-FET-PET for brain tumors, however, is still unknown. METHODS: We retrospectively analyzed 815 ^{18}F-FET-PET-scans from 391 patients using Standard-Uptake-Value calculations (SUVmax, SUVmean) and compared the results with MRI and/or histopathological findings. Using ROC curve analysis, we calculated the optimal SUV threshold value for a ^{18}F-FET positive lesion. RESULTS: The optimal threshold value for absolute ^{18}F-FET SUV was determined with 2.0 (sensitivity and specificity were 80% and 85%, respectively). Many lesions were found to be hypermetabolic on ^{18}F-FET-PET, including astro- and oligodendroglial tumors (= glioma group; n = 261 patients / 685 scans), other benign and malignant primary brain tumors (pilocytic astrocytoma WHO I, ependymoma WHO II-III, PNET/medulloblastoma/pinealoblastoma WHO IV, Primary CNS Lymphoma WHO IV), cerebral metastases, acoustic neurinoma, meningioma WHO I-II, tumor like-lesions (DNET, ganglioglioma, cavernoma), and active inflammatory (MS, ADEM, encephalitis), subacute ischemic (sinus vein thrombosis), and traumatic lesions (= non-glial lesion group; n = 130 / 130 scans). In glioma patients ^{18}F-FET-PET was able to identify hot spots of higher malignancy for surgery planning as well as post-surgery residual tumor burden for radiotherapy planning better than MRI. In addition, in the course of temozolomide and bevacizumab chemotherapy ^{18}FET-PET was helpful to discriminate between pseudoprogression / pseudoresponse and real tumor progression. CONCLUSIONS: ^{18}F-FET-PET hypermetabolism is detectable in various neoplastic, inflammatory, ischemic, and traumatic brain lesions, which limits the specificity of this method to identify tumors as gliomas. In patients with gliomas ^{18}F-FET-PET represents a helpful method for surgery and radiotherapy planning as well as for chemotherapy treatment monitoring.

NO-53. CENTRAL NEUROCYTOMA: TRANSSULCUS APPROACH FOR TOTAL EXCISION

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Central neurocytoma is a rare intraventricular tumor. The origin of the tumor is believed from the septum pellucidum. In MRI images, it is heterogeneous, and some part shows low enhancement. During the past 5 years, 12 patients with central neurocytoma were treated. Two image-diagnosed tumors were incidentally found during general health examination. Surgery was refused, and they received follow-up only. Slow growth was found in these two patients during 9 months and 2 years after diagnosis. A trans-sulcus approach was chosen to excise the large tumors (over 4.5 cm), and total excision was achieved in 8 patients. A small piece of tumor was left in a patient with an 8 cm long tumor. Only one tumor was excised through a transcallosal approach. One patient had tumor extending from right lateral ventricle through foramen Monro, third ventricle, and the aqueduct into fourth ventricle. It was removed without any neurological sequelae. Two patients had postoperative hemiparesis due to a basal ganglion infarct. One recovered after 6 months of rehabilitation. All of these tumors received abundant vascular supply from the thalamus. The early devascularization of blood supply from the thalamus and complete visualization of the tumor (especially the undersurface of corpus callosum) for easier total excision are the reasons the author preferred the trans-sulcus approach. There was no recurrence during the short follow-up (less than 5 years). The advantages and disadvantages of transcallosal and trans-sulcus approach will be discussed.

NO-54. INADVERTENT UNDERDOSING OF PATIENTS WITH NEOPLASTIC MENINGITIS: SHOOTING TO KILL OR GETTING SHOT IN THE FOOT

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INTRODUCTION: The mainstay of treatment for patients with neoplastic meningitis (NM) is intra-CSF chemotherapy administered through a ventricular reservoir. Numerous administration strategies have been advocated in the literature and are used in practice. This wide variation in practice suggests uncertainty regarding the optimal approach. Measuring the amount of radionuclide remaining in the delivery syringe, the butterfly tubing and needle, and the reservoir itself during the performance of CSF flow studies may provide data relevant to the efficiency of drug delivery. METHODS: Twenty patients with NM underwent conventional CSF flow studies using indium-111 DTPA. Four administration techniques that reflected published recommendations were used: 0.4 ml of radiopharmaceutical barbotaged with 10 ml of autologous CSF (2 patients); 3 or 5 ml of radiopharmaceutical barbotaged with 10 ml of CSF (3 and 4 patients, respectively) or not barbotaged but followed by repeated reservoir bulb compression (4 patients each); and 5 ml of radiopharmaceutical diluted with 5 ml of CSF, injected, and followed by repeated reservoir bulb compression (3 patients). Residual radionuclide counts were measured in the injection syringe, butterfly needle apparatus, and reservoir bulb. RESULTS: A substantial fraction of the injected dose remained in the reservoir bulb whenever a CSF flush was not used (mean 17.1%, range 8.6 - 57%) compared with a mean of 1.7% (range 0.44 - 3.1%) for all cases using a CSF flush (mean difference 15.4%, 95% CI 5.3 - 25.5, $p = 0.0049$). Residual radionuclide in the syringe and butterfly was negligible ($\leq 1\%$) in all cases. CONCLUSION: Many patients with NM are being inadvertently and substantially underdosed when receiving intra-CSF chemotherapy through a ventricular reservoir. Optimum administration requires placing drug in a total volume of 3-5 ml and barbotaging with 10 ml of autologous CSF.

NO-55. CHEMORADIATION-INDUCED THROMBOCYTOPENIA IMPACTS MORBIDITY AND MORTALITY IN NEWLY-DIAGNOSED HIGH-GRADE GLIOMA PATIENTS

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Although the literature points to <5% of high grade glioma (HGG) patients suffering from chemoradiation-induced thrombocytopenia, little is understood about how this side effect can impact treatment trajectory and survival. Since 2005, concurrent chemoradiation with temozolomide (TMZ) followed by dose-dense TMZ for 6 to 12 months has become the standard of care for WHO grade III/IV newly diagnosed gliomas. Current clinical recommendations advise interruption of therapy if thrombocytopenia develops. Using a retrospective design, we conducted a single-center chart review to evaluate patients with HGG who have developed thrombocytopenia (defined as a platelet count of less than 100 x 109/L) while receiving concurrent TMZ and radiation therapy either on or off clinical trials at the Preston Robert Tisch Brain Tumor Center at Duke from November 2007 until December 2010. A control group of patients undergoing similar therapy for HGG was randomly selected for comparison. Particular attention was given to time of onset and duration of thrombocytopenia, median platelet count nadir, platelet transfusion requirements, progression-free survival (PFS), and overall survival (OS). In our cohort of 20 thrombocytopenic patients, all experienced interruption or cessation of chemotherapy due to thrombocytopenia, and at present, they had a median PFS of 9.8 months and OS of 11.1 months. Currently, the control group who received full-scheduled chemoradiation therapy experienced a median PFS of 11.6 months and OS of 12.0 months. In the cohort of thrombocytopenic patients, the median platelet count nadir was 21 x 109/L (range 2 to 85 x 109/L). Median duration of the nadir was 14.5 days. 9 of 20 patients (45%) required at least 2 platelet transfusions during this time. Further research is warranted to understand morbidity and mortality in this population associated with thrombocytopenia and to investigate possible methods of intervention.

NO-56. PROLONGED ONE YEAR SYMPTOMATIC INTERVAL PRIOR TO DIAGNOSIS OF LEPTOMENINGEAL CARCINOMATOSIS IN A BREAST CANCER PATIENT

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CASE REPORT: A 58-year-old woman had been diagnosed 11 years previously with a multicentric grade II lobular carcinoma of the breast with 3/14 axillary nodes positive for cancer. The carcinoma was PR + /variable ER and HER-2 negative. She was treated with adriamycin and cytoxan X 4 cycles followed by taxotere and XRT to the chest wall and regional lymphatics followed by 5 years of tamoxifen. She was then NED for 5 years when she developed severe HA and projectile vomiting associated with hypoventilation requiring intubation for poor oxygen saturation. Spinal fluid was cloudy with a glucose of 42, elevated protein of 175, 32 white cells, 18 red cells. She was negative for West Nile virus and Lyme disease by rapid PCR. Her opening pressure was 280 cm. She was discharged without a diagnosis and for the next year had a recurrent symptom complex of drop attacks, severe tinnitus, muffled hearing, and diplopia. After 12 months, she developed papilledema in her left eye. PET scan showed no systemic disease apart from one small vertebral body metastasis. Leptomeningeal metastases (LMM) were confirmed by CSF cytology. The patient was begun on intrathecal cytarabine through an Ommaya reservoir and has remained normal with clearing of her CSF now 7 months later. CONCLUSION: A review of the literature of solid tumor leptomeningeal carcinomatosis suggests that breast cancer patients with limited systemic disease have the best prognosis, but we found no case in which untreated survival surpassed 3 months. Median survival of treated LMM from breast cancer can reach at least 6 months. Central hypoventilation and a prolonged clinical course are possible with LMM and need to be vigorously pursued, particularly in patients with breast cancer.

NO-57. CARCINOMATOSIS MENINGITIS ASSOCIATED WITH SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK

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INTRODUCTION: Carcinomatosis meningitis is a serious complication of metastatic cancers and often causes significant neurologic morbidity. Although it is most often associated with breast cancer, lung cancer, melanoma, and gastrointestinal malignancies, it has rarely been reported in cases of squamous cell carcinoma of the head and neck. METHODS: We report the clinical, imaging and histopathologic features of two cases of carcinomatosis meningitis associated with squamous cell carcinoma of the head and neck and present the results of a comprehensive literature review. RESULTS: A 72-year-old man developed a skin lesion above his left eyebrow that was later diagnosed as squamous cell carcinoma. Six months after diagnosis, he developed left forehead numbness, left abducens palsy, and left facial nerve palsy. MRI demonstrated thickening and enhancement of the affected cranial nerves, but CSF cytopathology did not reveal any malignant cells. He was treated with systemic cetuximab, carboplatin, and methotrexate as well as intrathecal thiotepa and focal radiation therapy. Two years after diagnosis, his carcinomatosis meningitis remains stable. A 67-year-old man developed a skin lesion on his left cheek that was subsequently diagnosed as squamous cell carcinoma. Three years later, he developed left facial numbness and weakness, and MRI demonstrated thickening and enhancement of the trigeminal and facial nerves. A biopsy demonstrated perineural involvement by carcinoma, but repeated lumbar punctures were negative for malignancy. He was treated with cetuximab, carboplatin, fluorouracil, and focal radiation therapy. His carcinomatosis meningitis later spread to involve multiple nerve roots. He died at ten years after diagnosis because of progression of disease. CONCLUSIONS: Carcinomatosis meningitis is a rare complication of squamous cell carcinoma of the head and neck. Clinical suspicion and imaging can support the diagnosis, and cytopathology of the CSF may be falsely negative. Biopsy can provide definitive diagnosis. Systemic and intrathecal chemotherapy, as well as radiation therapy, can be used as treatment.

NO-58. OUTCOMES IN PEDIATRIC AND ADULT CENTRAL NERVOUS SYSTEM (CNS) PRIMITIVE NEUROECTODERMAL TUMORS (PNET)

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PURPOSE: To compare outcomes for adult and pediatric patients treated for central nervous system (CNS) primitive neuro-ectodermal tumor (PNET) at a large academic center. METHODS: 25 patients with a diagnosis of PNET were retrospectively reviewed. Median age was 20. 14 patients were adults at diagnosis (age > 18). 21 PNETs were located in the brain, and 4 were elsewhere in the CNS (spine or meninges). All patients were staged with an MRI; 20 had an MRI of the spine for staging. 17 patients had M0 disease, 4 had M + , and M status was unknown (Mx) in 4 other cases. 6 patients had biopsies only, 5 had subtotal resections, 13 had gross total resections, and 1 had no surgery of the primary tumor. 12 patients were classified as high risk, 13 as standard risk. 21 patients received chemotherapy. All but 1 patient received radiation, and radiation records were available in all but 1 patient. 18 patients received craniospinal irradiation (CSI). Dose to the tumor bed was known for 18 patients, and the median was 5522 cGy (range 3600 to 6000). Overall survival (OS) and progression free survival (PFS) were estimated with Kaplan Meier curves. RESULTS: Median follow-up was 26 months. Estimated 3 year OS and PFS were 54% and 34%, respectively. 14 patients experienced treatment failure, most commonly in the vicinity of the original tumor (10 patients). PFS for adults was significantly worse than the pediatric cohort (23% vs. 53% at 3 years, $p = 0.03$). More adults had less than a GTR and were classified as high risk. Multivariate analysis was performed to account for the effect of risk category. PFS remained worse in adults when accounting for risk stratification in multivariate analysis ($P = 0.05$). CONCLUSIONS: Prognosis for adult patients with CNS PNETs is poor. Improved local control is necessary to improve outcomes in PNET.

NO-59. TREATMENT OUTCOME FOR 757 PATIENTS WITH GLIOBLASTOMA IN 3 POPULATION-BASED NEURO-ONCOLOGY CENTRES

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INTRODUCTION: Patients with glioblastoma multiforme (GBM) have historically had a median survival of 9-11 months after surgery and radiation therapy (RT). The addition of temozolomide (TMZ) to standard of care was supported by the 2005 Stupp study, which reported a median survival of 14.6 months. However, variation exists between and within patient populations. We examined 3 geographically distinct patient populations and evaluated the role of various prognostic factors. METHODS: Patients with GBM were identified at three Canadian centers in two Canadian provinces from prospectively collected databases of population-based neuro-oncology centers (years 2001-2008). Biopsy or extensive surgical debulking of the tumor was undertaken followed by RT, or RT with concomitant TMZ followed by 6-12 cycles of TMZ. MGMT promoter methylation status was assessed when possible. RESULTS: A total of 757 patients were analyzed from three centers: Calgary ($n = 352$), Edmonton ($n = 211$), and Halifax ($n = 194$). The mean age was 60 years, 64% were male, and the overall median survival was 9 months with no difference among sites ($p = 0.90$). The median survivals for methylated ($n = 172$) versus other methylation statuses ($n = 585$) was 12 versus 8 months, for debulking ($n = 485$) versus biopsy ($n = 272$) was 11 versus 5 months, and for RT + TMZ ($n = 423$) versus otherwise ($n = 334$) was 13 versus 4 months; $p < 0.001$. A wider gradient of median survivals was achieved by assigning a value of 1 for each of methylated, debulking, and RT + TMZ treatment and summing to a score between 0 and 3. The median survivals for patients scoring 0 ($n = 135$), 1 ($n = 254$), 2 ($n = 278$), and 3 ($n = 90$) were 3, 7, 12, and 19 months, respectively. CONCLUSION: Interesting similarities and differences were noted among the 3 centers, yet patient outcomes (median survival) were very comparable. Patients undergoing surgical debulking of methylated tumors who had both radiation therapy and chemotherapy had the best outcome (median survival 19 months).

NO-60. MOLECULAR SUBTYPING OF MEDULLOBLASTOMAS: INDIAN SCENARIO

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microRNA (miRNA) profiling of 19 medulloblastomas and four normal cerebellar tissues was carried out using a Taqman Low Density array v 1.0 which assesses 365 human miRNAs. In parallel, genome-wide expression profiling of protein coding genes was carried out using Affymetrix gene 1.0 ST arrays. Both profiling studies segregated medulloblastoma tumor tissues into four nearly identical molecular subtypes whereas normal cerebellar tissues segregated into a distinct group. A total of 43 medulloblastomas were analyzed for the expression of a select set of marker genes and miRNAs that were most significantly differentially expressed in the four molecular subtypes. Twelve out of 43 medulloblastomas in our study were found to carry mutations in the *CTNNB1* gene, which led to WNT pathway activation. Median age at diagnosis for WNT signaling-associated medulloblastomas is reported to be higher than that for all medulloblastomas. Median age at diagnosis of WNT signaling-associated tumors in our data set is

also high at 12 yrs. 4 out of 12 medulloblastoma patients belonging to the WNT cluster in our study are adults. Only four out of 43 medulloblastomas belonged to children less than three years age, which could explain the lower number (7 out of 43) of medulloblastomas with SHH signaling activation in our data set. Medulloblastomas associated with WNT signaling appear to be more common in the Indian subcontinent. This finding is being confirmed on a larger data set using paraffin embedded tumor tissues. A number of miRNAs including *miR-193a*, *miR-224/miR-452* cluster, *miR-182/miR-183/miR-96* cluster, *miR-204* and *miR-365* were found to be over-expressed in the WNT signaling-associated medulloblastomas. In the Daoy medulloblastoma cell line, over-expression of *miR-193a-3p* and *miR-204* using both miRNA mimics as well as the genomic region encoding the miRNAs was found to inhibit growth and reduce tumorigenicity of the cells.

NO-61. TUMOR-ASSOCIATED GLIAL CELLS PROMOTE GROWTH OF GBM XENOGRAFTS IN EGFP NOD/SCID MICE

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The recruitment of the host vasculature and the infiltrative behaviors of gliomas underscore the significance of tumor-stroma interactions in brain tumor pathogenesis. The aim of this project was to identify cancer-related changes in the stroma and their role during brain tumor progression. GBM biopsies were xenografted into green-fluorescent (GFP) NOD/Scid mice, which enabled us to separate stromal host cells (GFP^+) from human tumor cells (GFP^-) by fluorescence activated cell sorting (FACS). Endothelial and immune cells were excluded by their expression of CD31 and CD11b, respectively, during the sorting procedure. Control fluorescence microscopy and immunostaining for the pan-human specific marker HuNu confirmed a high purity (>95%) of the sorted cells and showed that the stromal cell population was highly enriched for glial markers. Microarray analysis of tumor-associated glial cells (TAGs) displayed a unique gene expression profile that was different from normal glial cells. Significantly, TAGs displayed an upregulation of genes associated with self-renewal, such as SOX2 and Musashi-1, as well as markers for immature cell types such as vimentin and NG2. TAGs from vascular tumors also expressed angiogenic factors, including VEGF, angiopoietin 2, and FGF2. Immunohistochemistry of mice brain tumor sections confirmed these findings as well as the presence of TAGs in the tumor bed. Notably, when cultured in stem cell medium, TAGs exhibited increased clonogenicity compared to glial cells isolated from normal mouse brain. Moreover, co-implanting TAGs with glioma cells accentuated the disease course, whereas implanting only glioma cells or glioma cells with unconditioned glial cells from normal mouse brain did not. Collectively, our findings implicate TAGs as critical regulators of brain tumor development and demonstrate that they co-evolve with glioma cells through stages which are closely associated with the stages of tumor progression. Moreover, these data establish TAGs as candidate targets for therapeutic intervention, potentially offering a new treatment approach for gliomas.

NO-62. PHASE II STUDY OF BEVACIZUMAB IN COMBINATION WITH DOSE-DENSE TEMOZOLOMIDE IN PATIENTS WITH RECURRENT GLIOBLASTOMA: PRELIMINARY SAFETY ANALYSIS

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Glioblastoma (GB) is among the most aggressive malignant brain tumors in the adult population. In recurrent GB, bevacizumab with irinotecan has demonstrated activity in phase II clinical trials; the combination has reported a significant improvement of RR, 6 month progression-free survival (PFS6), and overall survival (OS). There are limited data on safety and efficacy of bevacizumab in combination with other widely used chemotherapy agents such as temozolomide. The aim of this study is to evaluate the efficacy and safety of the combination of bevacizumab and dose-dense temozolomide. We report the safety profile of the first 10 patients treated in a Spanish phase II multicenter, open-label study in patients with recurrent GB treated with bevacizumab 10 mg/kg d 1 and 15 q28 until progression disease or unacceptable toxicity in combination with temozolomide 150 mg/m^2 week on/week off for 6 cycles. The primary endpoint of the study is PFS6. The toxicity was evaluated according to NCI CTC v3.0 criteria. From June 2010 to April 2011, 23 patients were included. An external expert and the study chair performed the safety analysis when the first 10 patients had received at least two treatment cycles. Treatment-related deaths, CNS bleedings, lymphopenia, thrombocytopenia, and neutropenia were mainly assessed. Patient characteristics were: median age 57.5 years (43-64), M/F: 4/6, ECOG 0-1 90%, totally/partially resected 4/6. All patients progressed after Stupp's regimen. At study entry, 7 patients were on dexamethasone with a median dose 6 mg (2-8 mg). Only 2 patients presented grade 3-4 adverse events: enteritis (1 patient, grade 3), intracranial hemorrhage (1, grade 4), upper respiratory infection (1, grade 3), urinary tract infection (1, grade 3), thrombosis (1, grade 3), and olfactory nerve disorder (1, grade 3). One patient had to stop the treatment because of an adverse event (intracranial hemorrhage). Treatment based in bevacizumab and a week on /week off temozolomide schedule shows an acceptable safety profile for treatment of recurrent GB. The study is ongoing.

NO-63. COMPARISON OF BEVACIZUMAB DOSE SCHEDULES FOR RECURRENT GLIOBLASTOMA

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INTRODUCTION: The FDA-approved schedule and dose of bevacizumab (BVZ) for recurrent glioblastoma (rGB) (10 mg/kg q 2 weeks) were adopted arbitrarily from certain colon cancer protocols. No dose defining studies have been performed for GB. We began using BVZ for treatment of rGB in 2005 at 5 mg/kg q 2 weeks combined with irinotecan and in the last 2 years as a single agent at the same dose. Our previous report of 20 patients treated with BVZ 5 mg/kg q 2 weeks showed similar response rate and overall survival (OS) to other BVZ treatment protocols with less adverse effects. In this study, we retrospectively reviewed our 6-year experience with BVZ in 125 rGB patients. OBJECTIVE: To compare treatment outcomes for BVZ doses of 5 mg/kg vs. 10 mg/kg. PATIENTS: 90 patients received BVZ at 5 mg/kg and 35 patients at 10 mg/kg. Median KPS and age were similar in both groups. There was a trend for prolonged survival in the 10 mg/kg group (281 vs. 193 days), although this difference was not statistically significant ($p = 0.136$). In a subgroup of patients who received BVZ as monotherapy (24 patients at 5 mg/kg and 22 at 10 mg/kg), the same trend for prolonged survival was observed for the higher dose (290 vs. 192 days; $p = 0.451$). Median OS was similar for groups treated with BVZ monotherapy at any dose vs. combined biochemotherapy (211.5 vs. 220 days; $p = 0.455$). Further analysis of the incidence of adverse effects in the respective subgroups will be reported. CONCLUSION: There is no significant difference in OS for rGB treated with BVZ doses of 5 mg/kg vs 10 mg/kg. The higher dose regimen was associated with a trend for prolonged OS. The addition of cytotoxic agents to BVC did not result in prolongation of OS.

NO-64. TRIPLE-NEGATIVE LOW-GRADE GLIOMAS: A HIGHLY AGGRESSIVE TUMOR WITH DISMAL PROGNOSIS

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BACKGROUND: The phenotypic heterogeneity of low-grade gliomas (LGGs) is still inconsistently explained by genetic alterations characteristic in patients treated according to present standards of care. Here we investigate the combined analysis of three molecular alterations according to clinical and radiologic data in a series of 89 LGGs to provide new insights into LGG pathogenesis. METHODS: *IDH1* codon 132 and *IDH2* codon 172 sequencing was performed in a series of 89 LGGs and correlated with clinical presentation, MR imaging characteristics, genomic profile, and outcome. Furthermore, p53 expression and 1p19q deletion status was assessed in all cases. RESULTS: A total of 74 IDH1 mutations at codon 132 and 2 IDH2 mutations at codon 172 were found, including 68 R132H (91.9%), 4 R132C (5.4%), 2 R132S (2.7%) and 2 R172M (5%). The *IDH* mutations were significantly associated with 1p19q deleted genotype ($P = 0.027$) and p53 expression ($P = 0.012$). The presence of *IDH* mutations was associated with a better outcome (5-year survival rate, 91% *v* 54%, respectively, $P < 0.001$) when compared to samples without *IDH* mutations. After adjustment for age, tumor location and size, radiologic infiltration pattern, and extent of surgery, multivariate analysis confirmed that the presence of *IDH* mutations was an independent favorable prognostic factor (hazard ratio = 34.6; 95% CI, 2.72 to 329.32, $P = 0.006$). Furthermore, we showed that patients

with tumors that lacked *IDH* mutations were significantly older ($P < 0.05$) and that these tumors involved significantly more frequently the insula ($P < 0.05$), were larger in size (>6cm, $P < 0.05$), displayed an infiltrative pattern on MRI ($P < 0.05$) and were almost all p53 negative with no 1p19q deletion ($P < 10^{-6}$). CONCLUSIONS: The combined absence of *IDH* mutations, p53 expression and 1p19 codeletion in LGGs identifies a novel entity coined "Triple negative" tumors with distinctive location, infiltrative behavior, specific molecular alterations and dismal outcome. These findings could significantly modify LGG classification and may represent a new tool to guide patient-tailored therapy.

NO-65. PROGNOSTIC SIGNIFICANCE OF MGMT PROMOTER METHYLATION STATUS IN ELDERLY PATIENTS WITH NEWLY DIAGNOSED GLIOBLASTOMA TREATED WITH BCNU WAFER IMPLANTATION: A PROSPECTIVE PATIENT COHORT

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BACKGROUND: The optimal treatment for elderly patients (age > 70 years) with glioblastoma (GBM) remains controversial. A recent randomized study conducted on newly diagnosed GBM patients demonstrated that concomitant and adjuvant temozolomide added to standard radiotherapy had a survival advantage compared with radiotherapy alone. The overall survival benefit of this aggressive treatment, however, was attenuated in older or patients with poor performance status. We assessed a prospective cohort of elderly patients (age >70 years) with GBM treated with BCNU wafer implantation, and we explored MGMT methylation status correlation with clinical outcome. METHODS: Newly diagnosed GBM patients (age > 70 years) were considered eligible. Treatment consisted in surgical resection with BCNU wafers implantation in all cases. Adjuvant radiotherapy was performed in 29 patients. MGMT methylation status was determined by a high-throughput quantitative methylation assay. The relationship between MGMT methylation status and survival was assessed with regard to other recognized prognostic factors. RESULTS: Median overall survival (OS) and progression-free survival (PFS) were 12.6 and 5.9 months, respectively. The 6-month and 12-month OS rates were 51% and 79%, respectively. PFS rates at 6 and 12 months were 40% and 4%, respectively. On multivariate analysis, Karnofsky performance status (KPS) ≥ 70 ($p = 0.005$) and MGMT hypermethylation ($p = 0.008$) were correlated with a better PFS. Also, KPS ≥ 70 ($p < 0.014$), MGMT hypermethylation ($p < 0.0001$), and age ≤ 80 ($p = 0.041$) were independently associated with a better OS. CONCLUSIONS: MGMT methylation status is an important prognostic factor in elderly patients treated with surgery plus BCNU wafer implantation for GBM and therefore is useful in predicting the outcome of GBM in this population.

NO-66. MULTIFOCAL INTRADURAL MENINGEAL METASTASIS ASSOCIATED WITH PILOCYTIC ASTROCYTOMA

Michael A. Errico and Lara J. Kunschner; Allegheny General Hospital, Pittsburgh, PA

Pilocytic astrocytoma or cystic cerebellar astrocytoma is predominately identified in young children and adults under the age of 20. Reported mean age of diagnosis in adults is 20 to 25 years. Pilocytic astrocytoma is classified by the World Health Organization as a grade-1 benign tumor. By definition a low-grade astrocytoma involving primarily the cerebellum, pilocytic astrocytoma may occur in other midline areas of the neuroaxis including the brainstem, third ventricle, hypothalamus, sellar region, optic chiasm, and rarely, the spinal cord. The most common symptoms on presentation are headache and seizure. Neurologic examination may reveal papilledema, gait ataxia, and hemiparesis. Less common findings include cranial nerve palsies, dysphagia, and behavioral changes. We report a case of a 54 year-old Caucasian female who presented with complaints of headache, neck stiffness, right upper extremity parasthesia, and mild confusion. Our patient had intermittent confusion episodes. Neurologic examination revealed papilledema and parasthesia of the face and upper extremities. Radiographic imaging, including MRI of the complete neuroaxis, and surgical biopsy were obtained for definitive diagnosis. MRI of the brain demonstrated a large fourth ventricular mass with extension into the cervical spine and hydrocephalus. MRI of the complete spine was completed and revealed multifocal areas of enhancing nodules at T2 and T3 and a nodular enhancing mass at the base of the thecal sac. She underwent a subtotal resection of the fourth ventricle mass with pathological report of a pilocytic astrocytoma. Subsequent ventriculoperitoneal shunting was performed in an attempt to relieve bilateral papilledema and ventriculomegaly. Since initial presentation, she has undergone re-resection after a surveillance MRI imaging demonstrated interval progression of the fourth ventricle mass despite radiation and chemotherapy. Pathologic specimens returned findings consistent with recurrent pilocytic astrocytoma without more malignant features noted.

NO-67. MULTIFOCAL INTRADURAL MENINGEAL METASTASIS ASSOCIATED WITH PILOCYTIC ASTROCYTOMA

Michael A. Errico and Lara J. Kunschner; Allegheny General Hospital, Pittsburgh, PA

Pilocytic astrocytoma or cystic cerebellar astrocytoma is predominately identified in young children and adults under the age of 20. Pilocytic astrocytoma is classified by the World Health Organization as a grade-1 benign tumor. By definition a low-grade astrocytoma involving primarily the cerebellum, pilocytic astrocytoma may occur in other midline areas of the neuroaxis including the brainstem, third ventricle, hypothalamus, sellar region, optic chiasm, and rarely, the spinal cord. The most common symptoms on presentation are headache and seizure. Neurologic examination may reveal papilledema, gait ataxia, and hemiparesis. Less common findings include cranial nerve palsies, dysphagia, and behavioral changes. We report a 25-year-old Caucasian male who developed left facial numbness after receiving a local injection to his lower lumbar region after an automobile accident. Initially a diagnosis of maxillary sinusitis was the cause of his facial numbness, and he was prescribed a course of antibiotics. After his symptoms failed to resolve, an MRI of his brain was performed. MRI of the brain demonstrated abnormal density in the suprasellar cistern that appeared to contact the optic chiasm. Lumbar puncture revealed elevated opening pressure of 450 mm H_2O without evidence of malignancy in the cytology. Fundoscopic examination revealed bilateral papilledema consistent with elevated intracranial pressure. He underwent ventriculoperitoneal shunting that improved his papilledema but failed to relieve his intermittent dizziness and increased lower lumbar pain that radiated to his right leg. Follow-up MRI of the brain and total spine revealed meningeal thickening from the cervicomedullary junction to the level of T12. Additionally, the entire thecal sac from L1 to the sacrum demonstrated meningeal thickening. No abnormal cord signal was identified. A thoracic laminectomy was performed, and pathology demonstrated low-grade glial neoplasm with leptomeningeal reaction. Based on clinical and histopathology examination, the intradural spinal neoplasm was thought to represent CSF drop metastasis from a pilocytic astrocytoma.

NO-68. PHASE II TRIAL OF BEVACIZUMAB WITH FOTEMUSTINE IN RECURRENT GLIOBLASTOMA: FINAL RESULTS OF A MULTICENTER STUDY OF AINO (ITALIAN ASSOCIATION OF NEURO-ONCOLOGY)

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INTRODUCTION: Bevacizumab (BV) has shown activity in recurrent glioblastoma (GBM), and few data are available on the combination of bevacizumab and nitrosoureas, which represent the standard cytotoxic options. Fotemustine (FTM) is a nitrosourea with elevated lipophilic properties. METHODS: In this phase II study, patients with GBM recurrent after surgery, radiation therapy, and concomitant/adjuvant temozolomide were eligible. The induction phase consisted of BV at 10 mg/kg intravenously on day 1 and 15 and FTM at 75mg/m2 intravenously on day 1 and 8, followed after a 3 week interval by a maintenance phase with BV at 10 mg/kg i.v. and FTM 75mg/ m2 every 3 weeks until tumor progression or unacceptable toxicity. Patients underwent clinical and MRI assessment 1 month after the start of treatment and every 2 months thereafter. The primary endpoint was progression-free survival at 6 months (PFS6), whereas secondary endpoints were response rate (RR), progression-free (PFS) and overall survival (OS), and safety. RESULTS: From April 2008 until November 2010, 54 patients were enrolled. PFS6, PFS12, and median PFS were 44%, 21% and 5.29 months, respectively. Median OS was 9.13 months with 77.4% and 31% of patients surviving at 6 and 12 months respectively. Response rates were as follows: 2 CR (4%), 24 PR (44%), 22 SD (41%) and 6 PD (11%). A significant neurological improvement was observed in 57% of patients, including steroids reduced or interrupted in 64%. 44/54 (81%) patients have progressed and patterns of progression were local in 29/44 (66%), multicentric in 10/44 (23%), gliomatosis in 3/44 (6%), and isolated leptomeningeal spread in 2/44 (5%). 12/54 (22%) patients with grade III/IV piastrinopenia/leukopenia discontinued FTM, whereas 4/54 (7.4%) discontinued BV (1 stroke, 1 intratumoral hemorrhage, 1 GI perforation, and 1

pulmonary embolism). CONCLUSION: BV + FTM in glioblastomas that recur after standard treatment is safe and promising. MGMT methylation data will be presented.

NO-69. AN OPEN LABEL, PROSPECTIVE, MULTICENTRIC STUDY TO EVALUATE THE SAFETY AND EFFICACY OF NIMOTUZUMABAS INDUCTION AND MAINTENANCE THERAPY IN COMBINATION WITH RADIOTHERAPY PLUS TEMOZOLOMIDE (CONCOMITANT & ADJUVANT) IN INDIAN PATIENTS WITH GLIOBLASTOMA MULTIFORME

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AIM: To evaluate the safety and efficacy of nimotuzumab (BIOMAb-EGFR) in combination with temozolomide and radiotherapy in glioblastoma. METHODS: Patients were accrued in an open-label, prospective, multicentric study for patients with glioblastoma. 56 suitable patients underwent four stages of treatment: concurrent, adjuvant, maintenance, and extended maintenance. Temozolomide (TMZ) was given 75 mg/m^2 daily for six weeks along with the study drug nimotuzumab in concurrent stages. Radiotherapy was given daily at 1.8 to 2 Gy per fraction five days a week for a total of 54-60 Gy. nimotuzumab 200 mg was continued every 3 weeks until disease progression or end of study (5 years). RESULTS: At a median follow-up period of 27.1 months, median overall and progression-free survival was 14.1 and 9.3 months, respectively. Median OS was 13.0 months in RPA Class V, 10.9 months in Class IV, and median OS was not applicable in Class III ($p = 0.0310$). Overall survival rates were 56.9% at the end of 1 year and 26.5% at 2 years in the ITT population. Class III subjects showed an OS of 100% at 1 year and 62.5% at 2 years. Class IV subjects had an OS of 30% at 1 year and 11.1% at 2 years. Class V patients had an OS of 54.5% at 1 year and 21.9% at 2 years. Out of 598 total adverse events, the majority were mild (315) or moderate (190) in severity. There were 27 life-threatening events or events including disease progression, grade 4 thrombocytopenia, grade 4 hyponatremia, convulsions, or similar outcomes. CONCLUSION: The results of this successful Indian multicentric study showed that adding nimotuzumab) to the standard of care (radiotherapy plus TMZ) appears to be encouraging in terms of PFS for patients with newly diagnosed GBM.

NO-70. EPSTEIN-BARR VIRUS (EBV)-DRIVEN CENTRAL NERVOUS SYSTEM LYMPHOMA (CNSL)

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We report 11 patients with positive CSF EBV PCR who were diagnosed with primary central nervous system lymphoma (PCNSL) and secondary CNSL from January 2000 to October 2010. Seven had PCNSL and 4 had secondary CNSL. Six patients (55%) were men. Median age at diagnosis was 46 (54 for PCNSL and 42 for secondary CNSL). All PCNSL patients had parenchymal brain disease; 5 had biopsy-confirmed DLBCL, 1 had kappa clonal excess on CSF flow cytometry, and 1 had clonal rearrangement of the immunoglobulin heavy chain gene in the CSF. All PCNSL patients had underlying immunosuppression [3 from HIV with low CD4 counts, 1 from allogeneic bone marrow transplant (BMT), 2 from solid organ transplants, and 1 from chronic corticosteroid therapy for autoimmune hepatitis]. Five patients received methotrexate-based chemotherapy. One patient with allogeneic BMT was treated with EBV-cytotoxic T-lymphocytes alone, and 1 HIV patient received whole brain radiation therapy alone. Median survival from diagnosis of PCNSL was 7 months (range 1-73 months) with 4 patients still alive. Of the 4 patients with secondary CNS lymphoma, 1 had diffuse large B-cell lymphoma, 1 had composite marginal zone and mantle cell lymphoma, 1 had HTLV1- associated T-cell lymphoma, and 1 had Burkitt's lymphoma. Three patients had active systemic disease at CNS relapse. Three had parenchymal brain involvement, and one had leptomeningeal disease. Two patients were immunosuppressed (1 HIV and 1 allogeneic BMT) before the diagnosis of lymphoma. Three patients received non-methotrexate systemic chemotherapy with intrathecal methotrexate. One patient received temozolomide alone because of poor performance status. All 4 patients died with a median survival from diagnosis of CNS relapse of 4 months (range 2-19 months). Two patients died of active CNS disease, one of active systemic disease, and one of neutropenic infection. EBV-driven lymphomas that involve the CNS have a worse prognosis than comparable non-EBV lymphomas.

NO-71. INTEGRATED MOLECULAR PROFILING OF ADULT AND PEDIATRIC PILOCYTIC ASTROCYTOMA THROUGH SINGLE NUCLEOTIDE POLYMORPHISM ARRAY AND GENE EXPRESSION ANALYSIS

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Pilocytic Astrocytoma (PA) is a Grade I Astrocytoma according to the WHO classification and is the most common brain tumor in children. Accounting for 23% of all pediatric brain tumors, PA occurs predominantly in infratentorial regions of the brain in pediatric patients and comprises about 80-85% of all tumors of the cerebellum in children. Recent studies have demonstrated key differences in the gene expression profiles of adult and pediatric glioblastoma multiforme (GBM), but molecular mechanisms important in PA tumorigenesis specific to adult and pediatric patients are largely uncharacterized. Therefore, we sought to profile key genetic characteristics of adult and pediatric PA tumors utilizing single nucleotide polymorphism (SNP) arrays. In addition, we used large-scale microarray-based gene expression profiling of adult and pediatric PA to characterize specific molecular mechanisms of putative importance in adult tumorigenesis versus that of pediatric PA. Upon integration, gene expression profiles can be correlated with genomic alterations that may better profile PA tumors on the basis of patient age, neuroanatomical location, and genotype. We have demonstrated, through SNP array analysis, that whole chromosome gain occurs more frequently, 63.6% vs. 15%, in adult versus pediatric PA, and that chromosomal gain occurred in all samples analyzed from supratentorial brain regions of adult patients. We also noted a high concomitant gain of chromosomes 5 and 7 in adult PA (36.4%) compared to pediatric tumor samples (5%). Gene expression profiling revealed distinct groups upon unsupervised clustering; it notably distinguished the gene expression profiles of pediatric and adult PA as well as on a neuroanatomical basis. Such differences in global gene expression may have roots in the large-scale genomic changes that distinguish PA with respect to age and brain location. We believe that integrated array-based analyses may allow us to more accurately profile adult and pediatric tumors and design more personalized patient therapy in clinic.

NO-72. INCREASED RISK OF CEREBRAL ATROPHY WITH PROLONGED BEVACIZUMAB ADMINISTRATION

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Bevacizumab (BEV), a monoclonal antibody against vascular endothelial growth factor (VEGF), is widely used as second-line treatment in patients with recurrent glioblastoma. Overall, BEV is well tolerated, and the most common adverse effects are hypertension and coagulopathy. Because BEV is well tolerated, treatment is commonly continued indefinitely in patients with stable disease. We present preliminary data on 14 patients treated with BEV for >9 months including 12 patients receiving treatment for >12 months. Of these patients, neuroradiology review revealed increasing atrophy in 8 of 14 patients (57%; 8 of 12 treated >12 months, 67%) after BEV initiation, with 5 of 8 (63%) developing diffuse cerebral atrophy beyond the radiation field. Patients were compared with respect to age, gender, overall survival, number of surgical interventions, total number and type of radiation treatments, number and type of chemotherapy regimens/agents administered prior to BEV initiation, elapsed time from completion of chemoradiation to BEV initiation, BEV treatment duration, number and type of agents used in combination with BEV, and number of underlying vascular/atrophy risk factors. There was a slight increase in the number of surgeries in the atrophy versus non-atrophy group (median 2 (1-3); median 1.5 (1-3), respectively), as well as in the total number of radiation treatments received (median 1.5 (1-2); median 1; (1-2), respectively). There was a more sizeable difference noted in the BEV treatment duration between atrophy and non-atrophy groups (median 87 weeks (54-166) and 56 weeks (43-106), respectively). There was also evidence of increasing cognitive dysfunction in the atrophy versus non-atrophy group at last follow-up (median mental status score (MSS) 1 (0-2); median MSS 0 (0-1), respectively). Although there are a number of limitations to a small, retrospective, imaging-based case series such as this, the data suggests an increased risk of cerebral atrophy and cognitive dysfunction with increasing duration of BEV treatment.

NO-73. TRIM11 IS A NOVEL AND SPECIFIC GLIOMA STEM-LIKE CELL MARKER THAT ALSO PLAYS A ROLE IN GLIOMA BIOLOGY THROUGH THE EGFR PATHWAY

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SUMMARY: Expression of tripartite motif-containing protein 11 (TRIM11), a member of the TRIM/RBCC family of E3 ubiquitin ligases, is upregulated in high grade glioma-derived tumor stem-like cells (GSCs) while remaining low in glioblastoma multiforme (GBM) cell lines, low-grade glioma-derived GSCs, and normal neural stem/progenitor cells (NSCs) studied *in vitro*. The expression pattern of *TRIM11* strongly correlated with that of the stem cell markers *CD133* and *nestin* in GSCs. Knockdown of TRIM11 inhibited proliferation, migration, and invasion of glioma cells and caused decreased EGFR levels and MAPK activity. These findings suggest that TRIM11 can be used to specifically identify and potentially target GBM-derived GSCs while selectively sparing normal NSCs and that TRIM11 also functions as an oncogene that promotes tumor growth and invasion. SIGNIFICANCE: GSCs are important for tumor initiation, resistance to conventional therapies, and tumor recurrence after therapy. Unfortunately, all reported markers for identifying and potentially targeting these cells are shared in common with normal NSCs. Damage to normal NSCs resulting from glioma therapies can produce profound cognitive side effects. The potential to selectively identify and target GSCs while sparing NSCs is an important advance. In addition, identifying TRIM11 as a novel new oncogene for malignant glioma with linkage into the EGFR signaling pathway expands our knowledge of TRIM11 biology and opens the door to exploring a potential new translational target for malignant glioma therapy. HIGHLIGHTS: 1) *TRIM11* is up-regulated in high-grade glioma GSCs, but not in low grade GSCs and NSCs studied in appropriate *in vitro* conditions relative to their cell type. 2) The expression pattern of *TRIM11* strongly correlates with that of *CD133* and *nestin* in GSCs. 3) TRIM11 promotes the proliferation, migration, and invasion of malignant glioma cells. 4) TRIM11 modulates EGFR expression, possibly through regulating the transcription of HB-EGF

NO-74. *IDH1* MUTATIONS IN GRADE II ASTROCYTOMAS ARE ASSOCIATED WITH UNFAVORABLE PROGRESSION-FREE SURVIVAL AND PROLONGED POST-RECURRENCE SURVIVAL

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The favorable prognostic impact of mutations in the *IDH1* gene is well documented for malignant gliomas; its influence on WHO grade II astrocytomas, however, is still under debate. A previously published database of 127 predominantly surgically treated patients harboring WHO grade II astrocytomas was revisited. Patients were screened for *TP53* mutations (sequencing analysis), *IDH1* mutations (pyrosequencing), and *MGMT* promoter methylation (methylation-specific polymerase-chain reaction (MSP) and bisulfite sequencing). Endpoints were overall survival (OS), progression-free survival (PFS), time to malignant transformation (TTM), and post-recurrence survival (PRS). Radiotherapy was usually withheld until tumor progression or malignant transformation occurred. *IDH1* mutations, *TP53* mutations, and methylated *MGMT* promoters were seen in 78.1%, 51.2%, and 80.0% of the analyzed tumors, respectively. *IDH1* mutations, which were significantly associated with *TP53* mutations and/or *MGMT* promoter methylation ($p < 0.001$), resulted in shortened PFS (median 47 vs. 84 months; $p = 0.004$); PRS, however, was significantly increased in those patients undergoing malignant transformation (median: 49 vs. 13.5 months; $p = 0.006$). Overall survival was not affected by *IDH1* mutation status. A similar pattern of influence was seen for *MGMT* promoter methylation: methylated tumors were associated with significantly worse outcomes in terms of PFS and better in terms of PRS; the low number of unmethylated tumors, however, limited the power of this analysis. Conversely, *TP53* mutations were strongly associated with a worse prognosis throughout the course of the disease. *IDH1* mutations are associated with a Janus Head-like phenomenon: unfavorable prognostic influence on PFS turns into favorable impact on PRS. A similar pattern of influence might exist for *MGMT* methylation.

NO-75. BRAIN METASTASIS FROM NON-SMALL CELL CANCER INITIALLY TREATED WITHOUT WHOLE BRAIN IRRADIATION: A RETROSPECTIVE ANALYSIS OF A CASE SERIES

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We sought to assess in patients with brain metastasis from NSCLC, survival from diagnosis of brain metastases (OSbm), and median cerebral progression-free survival (PFSc) at 6 and 12 months. We also sought to determine whether KPS <70 or ≥ 70, multiple or single brain metastases, age <50 or ≥ 50 years, synchronous or metachronous metastases, and gender impact PFSc and OSbm. Finally, we sought to determine site of relapse and cause of death. We analyzed 31 patients treated initially with surgery, radiosurgery, and/or focal radiotherapy with or without chemotherapy and without whole brain irradiation (WBI) from July 2007 to February 2011 with a minimum follow-up of 4 months. The median age was 58 years (36-77), and 14 patients were male. Median followup from diagnosis of brain metastases was 9 months (1-46). Ten patients had a solitary metastasis. PFSc and OSbm were calculated by Kaplan-Meier, and log rank test was used to test associations. INITIAL TREATMENT: 12 patients had surgery, 13 patients had surgery followed by radiosurgery, 8 patients had radiosurgery, and 1 patient had local radiation therapy. Seventeen patients (55%) had progression of CNS disease, of which 3 (9.6%) were only in the treated site, 4 (13%) in the initial site and distant within the CNS, and 12 (39%) only in a distant CNS site. Four patients underwent WBI at progression. Six-month PFSc and OSbm were 63% and 66%, respectively, and 12-month PFSc and OSbm were 27% and 53%, respectively. Median PFSc and OSbm were 8.6 months and 14 months. Statistically significant difference was found in OSbm in patients with KPS ≥ 70 ($p = 0.014$) compared to patients with KPS < 70. In 5 patients, the cause of death was neurological progression. The median OSbm was 14 months. Median PFSc was 8.6 months. The only statistically significant association was between OSbm and KPS ≥ 70.

NO-76. PERSONALIZING DRUG SCREENING FOR GLIOBLASTOMA MULTIFORME (GBM) PATIENTS

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After successfully culturing and expanding primary tumor cells from fresh brain tumor tissue samples, we screened the FDA-approved oncological drug set to find potent drugs for brain tumor patients. All positive drugs were already used in other kinds of cancer therapy, but not for brain tumors. For GBM patients, we personalized drugs based on the drug responses of in vitro screening. Another consideration is pharmaceutical features of the positive drugs, such as capability to penetrate the blood-brain barrier (BBB). We also investigated the mechanisms of successful drugs for GBM patients. Designing personalized treatments for GBM patients based on these results may make more rational chemotherapeutic strategies possible.

NO-77. THE EARLY EXPERIENCE WITH DR. BEAT: A PHASE IIA STUDY OF THE ADDITION OF TEMOZOLOMIDE TO A STANDARD CONDITIONING REGIMEN FOR AUTOLOGOUS STEM CELL TRANSPLANTATION IN RELAPSED AND REFRACTORY CENTRAL NERVOUS SYSTEM (CNS) LYMPHOMA

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This is a phase IIA, single institution trial to evaluate the safest dose of temozolomide that can be incorporated into a conditioning regimen (DRBEAT) for autologous hematopoietic stem cell transplant (ASCT) for relapsed or refractory primary central nervous system B cell lymphomas (PCNSL) or DLBCL with brain involvement. ASCT is rapidly becoming the standard of care for relapsed CNS lymphoma after high-dose methotrexate. The melphalan used in BEAM, a standard transplantation regimen, is thought to have poor CNS penetration. Temozolomide, an alkylating agent known to penetrate the CNS and approved by the FDA for brain tumors, is used frequently for relapsed/resistant CNS lymphomas. The most effective dose for this disease is unknown and dose-limiting toxicity is primarily thought secondary to bone marrow suppression. We sought to determine the maximum tolerated dose (MTD) using escalation with overdose controls (EWOC) as an adaptive dose-finding design. In our regimen, the D represents decadron, a steroid which is used as a standard premedication in the RBEAM regimen. The main difference between the RBEAM regimen and the DRBEAT regimen is the replacement of melphalan with temozolomide. Temozolomide is given as a daily dose either IV or PO over five days starting on day -5 of the ASCT. We are presenting the results of our first three patients dosed with an alpha .05 and theta .40 and treated

with escalating doses of 250, 287, and 351 mg/m2 daily x 5 days. To date, we have had no unexpected dose-limiting toxicity or difficulty with engraftment. Because of swallowing difficulty, we had utilized the IV formulation in one case. This is the first time to date we believe anyone has used EWOC in an ASCT protocol, and we will discuss the challenges in optimizing this technique for an ASCT for which DLTs are expected.

NO-78. TREATMENT OUTCOMES FOR PATIENTS WITH ANAPLASTIC ASTROCYTOMAS TREATED WITH RADIATION AND TEMOZOLOMIDE (TMZ) AND MAINTENANCE TMZ

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BACKGROUND: Patients with anaplastic astrocytomas (AAs) are either treated at diagnosis with radiation therapy and chemotherapy or chemoradiation using TMZ followed by maintenance TMZ. The optimal treatment regimen for patients with AAs is not defined, but studies are underway to determine this. We did a retrospective review of our patients with AA treated with chemoradiation using TMZ followed by maintenance TMZ and assessed for PFS-6, TTP, and OS. METHODS: We reviewed our database for patients diagnosed with an anaplastic glioma between 8/1/2003-6/15/2010 who were treated with using TMZ followed by maintenance TMZ. Our inclusion criteria included age > 18 yrs, newly diagnosed AA with no prior treatment, and sufficient data/follow up. Those without sufficient data were excluded. Data were analyzed to determine PFS, TTP, and OS. RESULTS: 28 patients were identified (14 men and 14 women) with a median age of 45 yrs (24-76) and median KPS of 90 (70-100). All patients were treated with chemoradiation, and 2 received arsenic trioxide during RT and 1 received avastin during the maintenance phase of TMZ. Identified pathologies included: AA (n = 23), AOA (n = 3), or anaplastic glioneuronal tumor (n = 2). The extent of resection was: GTR 25%, STR 57%, and biopsy 18%. The Median number of cycles was 10.5 (0-24). The median TTP was 18.5 months, and PFS-6, -12, and -24 were 96.1%, 73.1%, and 51.6%, respectively. Median OS was 34.4 months with OS at 12, 24, and 60 months of 92%, 63%, and 53.2%, respectively. CONCLUSIONS: There is currently no standard treatment for AAs. Data from NOA-04 indicate that initial treatment with chemotherapy or RT are the same, but how they compare with chemoradiation is unknown. Direct comparison to our study cannot be made, but our data is somewhat similar. Ongoing trials should help identify a standard AA treatment.

NO-79. MENINGIOMA RESPONSE TO BEVACIZUMAB: A RETROSPECTIVE ANALYSIS OF TREATMENT RESULTS IN 14 NF2 PATIENTS

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INTRODUCTION: Meningiomas are a major cause of morbidity and mortality in patients with neurofibromatosis 2 (NF2). No medical treatments are currently available for tumors that are not amenable to surgical resection or radiation therapy. Recently, we have demonstrated that bevacizumab, an anti-VEGF antibody, improves hearing function and decreases vestibular schwannoma (VS) size in some NF2 patients. METHODS: To determine the response of meningiomas to bevacizumab, we performed a retrospective analysis of 14 NF2 patients with meningiomas who were treated with bevacizumab for progressive VS between 2007 and 2010. Patients received bevacizumab 5 mg/kg i.v. every two weeks. Baseline MRI scans were performed approximately 1 month prior to the start of treatment, and followup MRI scans were performed every 3 - 6 months after therapy was initiated. A radiographic response was defined as ≥ 20% decrease in tumor volume compared with baseline measurements; progression was defined as ≥ 20% increase in volume from baseline measurements. All other responses were considered stable disease. RESULTS: Six men and eight women were treated with bevacizumab for a median of 15.5 months (range 6 - 36 months). The mean patient age was 29.5 years (range 16 to 63 years). A total of 40 meningiomas (mean 2.85/patient) were analyzed for response to therapy. A radiographic response was noted in 12/40 meningiomas (30%). Over the duration of this study, only seven tumors (17.5%) remained responsive, whereas 20 progressed (50%) and 13 remained stable (32.5%). There was no correlation between tumor response in a single patient; some meningiomas responded to therapy and others progressed in the same patient. CONCLUSION: Our results suggest that bevacizumab was effective in decreasing meningioma size in a minority of patients. A phase 2 study of bevacizumab in NF2 patients is ongoing and will help clarify the effect of bevacizumab treatment in this population.

NO-80. CONCURRENT BEVACIZUMAB (BEV), TEMOZOLOMIDE (TMZ), AND IRRADIATION (RT) IMPROVES SURVIVAL IN GLIOBLASTOMA PATIENTS COMPARED TO CONCURRENT RT AND TMZ RESERVING BEV AND TMZ FOR SALVAGE THERAPY

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PURPOSE/OBJECTIVES: Bevacizumab (BEV) is FDA-approved for treating the progression or recurrence of glioblastoma (GBM). We tested the hypothesis that integration of BEV into standard radiation (RT) with temozolomide (TMZ) improves progression-free survival (PFS) and overall survival (OS) compared to RT + TMZ alone. MATERIALS/METHODS: Under an IRB-approved protocol, we reviewed the treatment of 32 patients with GBM who received RT delivered either with concurrent and adjuvant BEV and TMZ (combined, n = 23) or TMZ alone (standard, n = 9). MRI scan with gadolinium was done before initiation of adjuvant therapy and every 3 months afterward. Patients received adjuvant therapy until either progression or 12 months after completion of RT. Progression was defined based on MRI changes, a change in therapy, death, or new clinical symptoms. All patients who progressed on standard therapy received BEV as salvage therapy. RESULTS: There was no significant difference between the combined and standard cohorts with respect to age, extent of resection, performance status, or radiation dose ($P > 0.05$). With a median follow up of 11 months, the median PFS was improved in the combined treatment cohort (9.4 months) when compared to the standard (4.1 months, $P < 0.001$). Median OS was not reached in the combined arm, whereas that of the standard arm was 13 months. The one-year survival rate was improved in the combined arm (72%) versus the standard arm with BEV as salvage (37%). CONCLUSION: Our results with standard RT + TMZ therapy are similar those reported by the EORTC/NCIC in terms of PFS and OS. The addition of BEV concurrently with RT + TMZ and as an adjuvant to TMZ improves PFS and OS. Reserving BEV for salvage therapy at the time of progression does not produce equal survival compared to concurrent administration.

NO-81. OUTCOME OF THE OLDEST OLD WITH PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA (PCNSL) AT MEMORIAL SLOAN-KETTERING CANCER CENTER (MSKCC)

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INTRODUCTION: Up to 20% of patients diagnosed with PCNSL are aged ≥ 80, yet optimal treatment for this growing demographic remains poorly defined. METHODS: This was a retrospective review of PCNSL patients diagnosed at age ≥ 80 and treated at MSKCC since 1993. Toxicity was analyzed by chart review, and response was determined by contrast-enhanced MRI. RESULTS: Sixteen patients (age 80-90) were identified with a median age of 81.5. Nine (56%) were women, and the median KPS at diagnosis was 50 (40-90). Fifteen patients (94%) received a median of 5 cycles of a methotrexate-based regimen. Baseline creatinine clearance ranged from 28-73 ml/min (median, 55). Twelve patients (75%) were treated with 3.5 g/m2 of MTX; reduced doses (1-3 g/m2) were used in the remaining three patients. One patient underwent upfront WBRT; a second received ocular RT and a third, spinal RT. Complete response was achieved in 7/16 patients (44%). Fifteen patients (94%) maintained or improved their baseline KPS over the course of treatment, and among responders, the median KPS after treatment was 90 (60-90). Ten patients (63%) returned home following MTX; one died of sepsis after his third cycle had cleared; and five (31%) were discharged to either a hospice or nursing home. One year survival rate from time of diagnosis was 25%; two year survival was 19% and three year survival 12.5%. Overall, chemotherapy was well tolerated. The most commonly observed MTX-related toxicity was bone marrow suppression, and only one patient experienced renal insufficiency requiring cessation of treatment after 4 of 5 planned cycles. CONCLUSIONS: High-dose methotrexate is feasible among select PCNSL patients aged ≥ 80 and may result in durable responses and improved KPS.

NO-82. PHASE II STUDY OF BEVACIZUMAB, TEMOZOLOMIDE, AND HYPOFRACTIONATED STEREOTACTIC RADIOTHERAPY (HFSRT) FOR NEWLY DIAGNOSED GLIOBLASTOMA

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BACKGROUND: The addition of bevacizumab allows for more aggressive RT schedules such as HFSRT. We initiated a phase II trial in newly diagnosed glioblastoma utilizing HFSRT, bevacizumab, and temozolomide. METHODS: Patients with tumor volumes less than 60cc were eligible. HFSRT was given in 6 treatments over 2 weeks: 6x6 Gy to the contrast-enhancing tumor and 6x4 Gy to the FLAIR hypersignal with dose painting concomitant with bevacizumab (10 mg/kg Q2 weeks) and temozolomide (75mg/m2 daily) and followed by adjuvant bevacizumab/ temozolomide (150-200 mg/m2 in 5/28 days). Followup included perfusion MRI (PWI) and neuropsychological assessment (NPA). Primary endpoint was 1-year overall survival (OS): promising: 70%, non-promising: 50%; α and $\beta = 0.1$. RESULTS: Accrual was completed ($N = 40$ evaluable patients; 14 women; median age: 55 years; median KPS: 90). The tumor's MGMT promoter was methylated in 23% and unmethylated in 77% of samples. Grades 3-4 nonhematologic toxicities included pulmonary embolism (2), renal failure (1), wound infection (1), and colitis (1); one patient died on study from an unknown cause. The median progression-free survival (PFS) was 11 months (95%CI 9-15). No patient had pseudoprogression. Among 30 evaluable patients, response (Macdonald criteria) was complete in 27%, partial in 63%; disease was stable in 3% and 7% progressed. The 1-year and 2-year OS were 89% (CI 74-95) and 31% (CI 13-56), respectively; median OS was 17.4m (CI 13-24) and median followup 15 months. NPA showed no statistically significant changes at 4 and 8 months followup. PWI showed early decreases in relative cerebral blood volume (rCBV): the mean baseline rCBV was 2.77 versus 1.65 at 6 weeks ($p = 0.01$). CONCLUSIONS: Results suggest that this aggressive RT schedule was safe and more convenient for patients (shorter treatment, high response rates, preserved cognitive function). In spite of a high frequency of unmethylated MGMT tumors, PFS and OS were comparable to temozolomide/bevacizumab with standard radiotherapy and contemporary historical controls, which warrants further investigation in the randomized setting.

NO-83. HFE GENOTYPE PREDICTS PATIENT SURVIVAL IN GLIOBLASTOMA MULTIFORME INDEPENDENT OF IDH1 GENOTYPE

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The HFE protein plays a key role in the regulation of cellular iron uptake. Cancer cells have a robust iron appetite, and therefore, it is logical that mutations in proteins that regulate cellular iron could impact cancer cell phenotype. HFE polymorphisms are common genetic variants in Caucasians. Mutations at amino acid site 63 (H63D) and 282 (C282Y) are the two most common HFE gene variants and result in increased iron accumulation in cells. We have previously reported that human astrocytoma and neuroblastoma cell lines are resistant to temodar and radiation. Therefore, we predicted that HFE polymorphisms would impact survival in patients with glioblastoma multiforme (GBM). The length of survival was defined as the time from the date of diagnosis to the date of death. The 1-year survival in GBM patients ($n = 56$) was significantly different between wild-type (WT) patients and H63D carriers. All H63D-carrying GBM patients died within a year of diagnosis. In addition, the median survival of male GBM patients with H63D mutation is shorter than that of male GBM patients with wild type HFE. NADP(+)-dependent isocitrate dehydrogenase 1 (*IDH1*) genotype is also reportedly correlated with survival of GBM patients. We are in the process of evaluating our GBM patients for *IDH1* genotype and to date, 29 have the wild type form of *IDH1*; the impact of HFE polymorphism status appears independent of IDH1. These data indicate that H63D HFE polymorphism is associated with poor GBM patient survival.

NO-84. INFLUENCE OF FLUORETHYLTYROSIN-POSITRON-TOMOGRAPHY (FET-PET) IN THE DAILY ROUTINE DECISIONMAKING PROCESS OF THE THERAPY OF RECURRENT MALIGNANT GLIOMA

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INTRODUCTION: Imaging techniques are important for accurate diagnosis and follow-up. T1-weighted MRI is the gold standard. However, this technique reflects biological activity of the tumor. Fluoroethyltyrosine (FET) is an amino acid marker with high specificity for tumor metabolism. We evaluated the influence of FET-PET for detecting the recurrence of WHO grade IV gliomas and a malignisation of WHO-Grade III gliomas. METHODS: FET-PET studies were performed on 18 glioma patients (8 patients with glioblastoma multiforme WHO Grade IV and 10 patients with glioma WHO grade III). All patients underwent magnetic resonance imaging (MRI) +/− gadolinium) and FET-PET. FET-PET testing was performed by the Research Center Jülich. We assessed the tumor's maximal standardized uptake value (SUVmax) and the ratio to the background. Histopathological findings were matched to the results of both diagnostic tools. RESULTS: In 36% (4/10) of the WHO-grade III glioma patients, FET-PET was positive. The histopathological findings showed a recurrence of the tumor and/or a malignisation to WHO Grade IV. In 50% (4/8) of the glioblastoma patients, treatment with surgery and radio-chemotherapy (RCX) showed a significant contrast enhancement (MRI+), and PET was positive. PET + -area was larger than contrast enhancement area in the MRI. Histopathological results showed a correspondence between the PET+ area and the tumor recurrence area. CONCLUSION: Additional metabolic information was provided by FET-PET. In our study, FET-PET had a significant influence on the decision to perform an operation or biopsy in patients with suspicion of tumor recurrence and size of tumor recurrence. In these cases, PET gave us detailed information about the extent of tumor tissue and potential for malignant transformation.

NO-85. LONG-TERM SAFETY AND EFFICACY RESULTS OF ORAL EVEROLIMUS IN PATIENTS WITH SUBEPENDYMAL GIANT CELL ASTROCYTOMAS (SEGA) IN TUBEROUS SCLEROSIS COMPLEX (TSC)

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Patients with TSC develop a variety of benign tubers in multiple organ systems. In the CNS, manifestations include SEGA, cortical tubers, epilepsy, and neurocognitive and behavioral problems. In a phase 1/2 study in patients with SEGA associated with TSC, the mammalian target of rapamycin (mTOR) inhibitor everolimus significantly reduced SEGA volume within a few months without the need for surgical intervention (Krueger et al. NEJM 2010;363:1801-1811). Seizure frequency also decreased. The study is in an open-label extension phase to determine the long-term safety and efficacy of oral everolimus (titrated to achieve a target trough concentration of 5-15 ng/mL) treatment in these patients. Of 28 patients enrolled in the initial study, 25 were still receiving everolimus at the extension study cut-off date (31-Dec-2010). Median treatment duration was 1041 days (range, 142-1434), and the median dose was 5.29 mg/m^2/day (range, 2.1-12.3). Reduction of the primary SEGA volume by $\geq$30% from baseline occurred in 79.2%, 64.7%, and 77.8% of patients at 24, 30, and 36 months, respectively and reduction of SEGA by $\geq$50% from baseline in 50%, 41.2%, and 55.6% of patients at 24, 30, and 36 months. The $\geq$30% reduction in primary SEGA volume was maintained for a median of 23.8 months (up to progression or the cut-off date). Adverse events (AEs) were mostly grade 1/2 in severity and were consistent with those previously reported. Over the duration of the entire study, single cases of grade 3 drug-related AEs (stomatitis, sinusitis, viral bronchitis, and concomitant neutropenia) were reported at $<$12 months, 25-36 months (stomatitis, pneumonia, and limb abscess), and $>$36 months (neutropenia). No drug-related grade 4 events were reported, and no AE led to the discontinuation of everolimus. This study confirmed that long-term treatment with everolimus is safe and effective for patients with SEGA associated with TSC; SEGA volume reductions have been maintained in patients receiving everolimus for up to 3 years.

NO-86. A PHASE I TRIAL OF LAROMUSTINE (VNP40101M) AND TEMOZOLOMIDE FOR PATIENTS WITH MALIGNANT GLIOMAS IN FIRST RELAPSE OR PROGRESSION

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BACKGROUND: Effective treatments for recurrent malignant gliomas are limited. MGMT is one of the mechanisms of resistance for malignant gliomas. Depletion of MGMT may improve anti-tumor activity by increasing the activity of alkylators. We used this concept to perform a phase I trial of temozolomide (TMZ) and chloretazine. METHODS: Patients were enrolled in a standard 3 + 3 phase I trial with the goal of performing a phase II trial at the MTD. Patients were treated with TMZ at 75 mg/m^2 on days 1-7 and then chloretazine at 100, 150, or 125mg/m^2 on day 7 (2 hours after TMZ) for a 6 week cycle. Patients were treated until progression or intolerable side effects. Patients had MRI scans every 6 weeks with a physical exam and weekly CBC. RESULTS: A total of 14 patients were accrued (10 GBM, 3

AA, and 1 AOA): 10 men and 4 women with a median age of 51 (25-68) and KPS of 90 (80-100). The median number of cycles was 1 (1-4). Dose level 100 mg/m^2 had 7 patients with 1 grade 4 thrombocytopenia; dose level 150 mg/m^2 had 5 patients with 1 grade 4 thrombocytopenia and 1 grade 3 fatigue. Dose level 125 mg/m^2 had 2 patients with 1 grade 4 leukopenia and 1 grade 4 thrombocytopenia. 10 patients had PD after 1 cycle, and 4 were removed for toxicity. 3 patients who did not progress had SD. PFS-6 was 7%. CONCLUSION: The optimal dose for phase II was felt to be TMZ 75 mg/m2 x 7 days and chloretazine 100 mg/m^2 on day 7. The main toxicity of this regimen, which attempted to take advantage of an MGMT depletion strategy, was myelosuppression. Myelosuppression is a limiting toxicity in several studies utilizing this approach, which suggests that it may not be feasible.

NO-87. BEVACIZUMAB IN MULTIPLY RECURRENT AGGRESSIVE MENINGIOMAS

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BACKGROUND: Patients with atypical and anaplastic meningiomas may experience tumor progression in spite of standard treatment with surgery and radiotherapy. No chemotherapy has proven effective in this setting; the 6-month progression free survival for WHO grade II/III meningiomas is nearly 0%. Meningiomas are highly vascular tumors and display high expression of vascular endothelial growth factor (VEGF), a fact that provides the rationale for exploring treatments such as the anti-VEGF monoclonal antibody bevacizumab. METHODS: We retrospectively reviewed the records of nine patients with WHO grade II and III multiply recurrent meningiomas who received antiangiogenic therapy with bevacizumab. We focused on progression free survival, overall survival, radiographic response, and toxicity. RESULTS: Nine patients (4 women) with a median age of 52 years (range, 34-81) received treatment with bevacizumab for Grade II or III meningioma. Four patients had pathological diagnosis of atypical (Grade II) meningioma, and 5 had anaplastic (Grade III) meningioma. All patients had received prior surgery and radiation and were not candidates for either. Bevacizumab was administered at 10mg/kg every 2 weeks for a median of 7 treatments (range, 1-16). The best radiographic response was a minor size reduction in three (<50% reduction in tumor) and stable disease in five patients; scan is pending in 1 patient. At a median follow-up of 7 months (range 2-22), 2 patients progressed and died. Seven patients are alive, 2 of whom developed intratumoral hemorrhage; bevacizumab was discontinued in these 2 patients. CONCLUSION: Antiangiogenic therapy may be an effective strategy for treatment of recurrent meningiomas that are ineligible for further surgery and radiotherapy. Two patients developed nonfatal intratumoral hemorrhage after receiving bevacizumab. Further studies are needed to determine the safety and efficacy of bevacizumab in this setting.

NO-88. BEVACIZUMAB FOR TREATMENT OF RECURRENT GANGLIOGLIOMA

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Gangliogliomas are tumors that have glial and neuronal components and are known to have benign histology with a favorable prognosis (1). Treatment is surgical, and gross-total resection is curative (1,2). Radiation therapy is reserved for recurrences or malignant transformation. There is little evidence for chemotherapy, but there are case reports of successful treatment of congenital malignant gangliogliomas and pediatric low grade progressive gangliogliomas with carboplatin alone or in combination with etoposide (3,4,5).We describe a case of a 23 year old man with recurrent left temporal lobe ganglioglioma treated with bevacizumab. Bevacizumab is a humanized monoclonal antibody that inhibits the activity of vascular endothelial growth factor and has been used in the treatment of glioblastoma multiforme (6,7). The patient was diagnosed 7 years ago after presenting with headaches and seizures. He underwent subtotal resection. Three years later, he had radiographic progression, and pathology revealed recurrent ganglioglioma with the glial component showing oligodendroglial features. FISH testing showed intact 1p and 19q chromosomes. The patient received involved-field radiation therapy (54 Gy). He was stable for 3 years, but then had headaches and was found to have radiographic recurrence. Another subtotal resection was done, and the pathology revealed recurrent ganglioglioma. Three months after his surgery, he had radiographic recurrence, and he was treated with temozolomide (200 mg/m2). He tolerated the therapy well, but he had recurrence of partial seizures. MRI after the third cycle of temozolomide showed tumor progression. The patient was started on bevacizumab monotherapy (10 mg/kg every 2 weeks). He tolerated the treatment well but had blood pressure elevation, which was effectively treated with amlodipine. After two cycles, the seizures were controlled, and MRI revealed an almost complete resolution of the enhancing lesion (partial response by RANO criteria (8)). Bevacizumab appears to be a tolerable and effective treatment for recurrent progressive ganglioglioma.

NO-89. A PHASE I STUDY OF SORAFENIB WITH RADIATION AND TEMOZOLOMIDE IN NEWLY DIAGNOSED GLIOBLASTOMA

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Increased angiogenesis and activation of the MAP kinase pathway are associated with poor prognosis in glioblastoma (GBM). Sorafenib is a multifunctional small molecule inhibitor that targets both the Raf/MAP kinase pathway and VEGF receptors and is thus a potentially attractive agent for overcoming resistance to standard therapy. We conducted a Phase I study to determine the maximum tolerated dose (MTD) and toxicity profile of sorafenib given both concurrently with chemoradiation and in the adjuvant setting along with standard dose temozolomide. Dose Level 1 consisted of Sorafenib (400mg BID) given after radiation therapy along with standard dose adjuvant temozolomide. A total of 10 patients were enrolled, of which 6 were evaluable. One DLT was observed (grade 3 wound dehiscence), although dose reductions were needed in subsequent cycles in approximately 50% of patients. Dose Level 2 consisted of sorafenib (200mg BID) given daily during radiation therapy and concurrent temozolomide and followed by sorafenib (400mg BID) given after radiation therapy with temozolomide. At this dose level, a total of 8 patients were enrolled, of which 6 were evaluable. A total of 3 DLTs were observed, including grade 3 rash and hematoma and grade 4 decreased hemoglobin, which indicated a breach of the MTD. In terms of patient outcomes, two patients at Dose Level 1 completed 12 cycles of adjuvant temozolomide and sorafenib without progression, whereas two other patients progressed during the initial 12 months. The remaining patients are continuing treatment without evidence of progression. Although the progression-free survival outcomes observed to date are promising and will be updated as time proceeds, we conclude based on current results that the combination of sorafenib with standard chemoradiation and adjuvant temozolomide is associated with significant toxicities (particularly during the chemoradiation portion) without a striking clinical benefit, and the decision was made not to pursue a Phase II study at this time.

NO-90. THE DIMINISHING IMPACT OF AGE AS A PROGNOSTIC FACTOR FOR GLIOBLASTOMA PATIENTS IN THE ERA OF BEVACIZUMAB

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Multiple studies identify old age as a negative prognostic factor in glioblastoma. As a result, practicing physicians may be nihilistic in their approach to treating elderly patients, and clinical trials routinely restrict enrollment after age 70. We have noted that the impact of age seems less powerful since the introduction of bevacizumab (BEV) and conducted a retrospective analysis of 185 glioblastoma patients ranging from 22 to 93 years old to assess this impression. All patients were treated at our center from 2004 to 2010; 75 of these patients received BEV. In the total cohort, overall survival was longer in patients who received BEV (20.8 v 10.1 months, $p < 0.001$ log rank). This survival benefit was also significant in patients >70 receiving BEV (12.4 vs. 4 months, $p < 0.001$ log rank). In the group that did not receive BEV, the difference in survival between patients stratified according to age groups <50, 50-69, and >70 was statistically significant (medians 13.5, 15.1, and 4.0 months, respectively; <0.001, log rank). In patients who received BEV, there was no significant difference between the age groups (22.2, 21.1, and 12.4 months, $p = 0.24$ NS, log rank). Based on these data, we conclude that the introduction of BEV has diminished the impact of age on outcome and suggest that the practice of excluding patients from trials solely on the basis of age should be reconsidered.

NO-91. RECURRENT PAPILLARY TUMOR OF THE PINEAL REGION (PTPR) IN A PEDIATRIC PATIENT: A BRIEF REPORT

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Papillary tumors of the pineal region are rare tumors arising from the specialized ependyma of the subcommissural region and represent < 1% of all intracranial tumors. Immunohistochemistry helps to differentiate these from closely related choroid plexus tumors and papillary ependymomas. We report a child with a recurrent papillary tumor of the pineal gland and highlight the distinct clinicopathological features of this tumor. The patient presented at 11 years of age with a one-month history of nausea, vomiting, headache, and vision changes. MRI revealed a 2 cm mass in the pineal region with obstructive hydrocephalus. He underwent an endoscopic third ventriculostomy with biopsy of the tumor. Pathology revealed a highly cellular tumor with papillary and perivascular arrangement and a mitotic index of 30-40%. The tumor was immunoreactive for cytokeratin and vimentin, which is consistent with a diagnosis of papillary tumor of the pineal region. Gross total resection of the tumor (GTR) was performed. He presented with local recurrences 3 years and 5 years from initial diagnosis with symptoms of increasing headache and diplopia. MRI confirmed local recurrences in the pineal region with obstructive hydrocephalus in both instances. GTR was performed after both recurrences. Mitotic index in the recurrent tumor specimens had increased to 50-60%. Adjuvant radiotherapy (54 cGY to the tumor bed) was given after the 2nd recurrence. Nine patients < 18 years of age with PTPR have been described in the literature to date. This tumor type is prone to local recurrences and may disseminate to the spine. Maximum surgical resection is the treatment of choice. In a review of 31 patients by Montange et al., 5 year overall survival was 73% and progression free survival was 27%. The potential role of radiotherapy and chemotherapy needs to be addressed for these rare tumors.

NO-92. PEMETREXED FOR PATIENTS WITH CENTRAL NERVOUS SYSTEM (CNS) METASTASES

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BACKGROUND: Treatment options for patients with CNS solid tumor metastases after WBRT are limited. Pemetrexed is a multitargeted antifolate agent approved for NSCLC with activity seen in several solid tumors. We performed two separate trials using pemetrexed to treat CNS metastases. METHODS: IRB approved consent was obtained in patients with solid tumor CNS metastases. These patients were in one of two trials and given one of four dose levels of pemetrexed: 500 (n = 5), 750 (n = 3), 900 (n = 13), or 1050 mg/m^2 (n = 3) once every 3 weeks (1 cycle + 6 weeks). Patients received pretreatment folic acid and B12 injections and continued on treatment until disease progression or the treatment could no longer be tolerated. RESULTS: Twenty-one patients (15 women, 6 men) with a median age of 50 (range 26-70) and median KPS 90 (range 60-100) were treated. Primary tumor sites included breast (13), lung (4), colon (1), endometrial (1), esophageal (1), and pinealoblastoma (1). Patients received a median of 3 (range 1-14) doses. Partial response was seen in 1 (breast), stable disease in 10 (6 breast, 2 lung, 1 pinealoblastoma, 1 endometrial), and progressive disease in 10. Grade 3/4 toxicities were mostly myelosuppressive and seen in 7 patients. Median TTP and OS were 2.7 and 8.5 months, respectively; PFS-6 was 17.65%. Breast cancer subset patients had median TTP and OS of 2.7 and 8 months; PFS-6 for this subset was 20%. CONCLUSION: Pemetrexed is tolerated in patients with solid tumor CNS metastases. Although the population studied was small, antitumor activity is observed in 50% of patients (primarily breast) with most achieving disease stabilization.

NO-93. NCCTG PHASE II TRIAL OF BEVACIZUMAB IN COMBINATION WITH SORAFENIB (BEV/SOR) IN RECURRENT GLIOBLASTOMA (rGBM)

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We hypothesized that vertical blockade of VEGF signaling by combining bevacizumab/sorafenib (ligand/receptor targeting) in rGBM patients would have a synergistic therapeutic effect. We also investigated whether MR imaging (DSE perfusion and DCE permeability), VEGF, VEGFR2, and HIF-1a SNPs, and/or circulating markers of angiogenesis [i.e., circulating endothelial cells (CECs), bFGF, or SDF-1α] correlated with treatment efficacy and/or toxicity. METHODS: Recurrent GBM patients who had received ≤ 1 regimens for progressive disease were eligible. Patients received bevacizumab (5 mg/kg every 2 weeks) with sorafenib (200 mg bid, weekly, days 1-5) (Group A), but because of toxicity, the starting sorafenib dose was subsequently modified to 200 mg qd (Group B). RESULTS: Fifty-four patients were enrolled: 19 patients in Group A and 35 in Group B. Overall objective response rate was 18.5% with a median duration of 6.7 months (range 0.5-24.1 months). The study did not meet its primary efficacy endpoint with only 11/54 (20.4%) patients experiencing progression-free survival at 6 months after treatment. Median PFS was 2.9 months (95% CI: 2.3-3.6), and median OS was 5.6 months (95% CI 4.7 - 8.2). Outcome was similar between the two dose groups. Incidence of ≥ grade 3 nonhematologic toxicity in the first two treatment cycles did not improve with reduced sorafenib dose, but fewer patients discontinued treatment early because of toxicity (14% vs 31.5%). VEGF/VEGFR SNPs were associated with PFS ($p < 0.022$). CECs, bFGF, or SDF-1α were not correlated with PFS6, although a $\log_2$-fold decrease in CECs during treatment was observed with subsequent increase at progression. A >25% decrease in ADC from baseline to the 4 week followup MR scan was associated with increased PFS ($p = 0.012$) and OS (0.018). CONCLUSIONS: Although the BEV/SOR combination didn't improve patient outcome versus historic BEV-treated controls, the significance of ADC imaging changes and VEGF/ VEGFR SNPs in defining subsets of patients that may benefit from antiangiogenesis treatment merits further investigation.

NO-94. BEVACIZUMAB FOR THE TREATMENT OF SURGICALLY UNRESECTABLE CERVICAL CORD HEMANGIOBLASTOMA

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Hemangioblastomas of the central nervous system commonly arise in the cerebellum and less commonly in the spinal cord. They express high levels of vascular endothelial growth factor (VEGF) and are therefore highly vascular tumors. Bevacizumab is a targeted agent that blocks tumor angiogenesis through inhibition of the VEGF ligand-receptor interaction. Here we show that bevacizumab can be an effective treatment approach for surgically unresectable spinal cord hemangioblastoma. A 52 year old patient with surgically unresectable cervical cord hemangioblastoma and progressive quadriparesis was successfully treated with bevacizumab. After 6 cycles of bevacizumab, his tumor decreased in size from 2.7 x 1.0 x 1.5 cm to 2.0 x 0.8 x 1.5 cm as determined by MRI with contrast. To the best of our knowledge, this has never been reported in the past.

NO-95. TIME TRENDS IN TREATMENT OF ANAPLASTIC OLIGODENDROGLIAL TUMORS

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INTRODUCTION: Treatment recommendations for newly diagnosed anaplastic oligodendroglioma (AO) or oligo-astrocytoma (AOA) vary widely. We sought to describe actual treatment over 3 decades and explore clinical correlates of administered therapies. METHODS: We previously conducted an international retrospective study of adults diagnosed 1981-2007 who were not enrolled on phase III trials for newly diagnosed

disease to capture the outcomes of commonly administered initial therapies. We analyzed time trends in treatment during the study period. Correlates of specific strategies delivered were assessed using a logistic regression model. RESULTS: Among 1013 patients, there was a marked increase in the utilization of chemotherapy over time. Before 1985, 67% of patients received radiotherapy alone compared to only 5% since 2005. Similarly, treatment with chemotherapy alone increased from 0% before 1985 to 38% since 2005. Among patients receiving chemotherapy alone, temozolomide replaced PCV (0% temozolomide, 86% PCV in 1995-1999; 98% temozolomide, 2% PCV since 2005). The change from PCV to temozolomide was also observed among patients who received radiotherapy and chemotherapy sequentially and/or concurrently. These differences were highly significant ($p < 0.0001$). Treatment patterns varied substantially by 1p19q deletion status and histologic subtype: cases with no 1p19q deletion, AOA histology, and frontal lobe tumors were most likely to receive radiotherapy and chemotherapy (with temozolomide). Those with 1p19q codeletion, pure AO histology, and without debulking surgery were more likely to receive chemotherapy alone. CONCLUSIONS: Treatment patterns have changed significantly over time with increased administration of chemotherapy (alone or with radiotherapy), and temozolomide replaced PCV, despite an absence of definitive data from randomized trials. Ongoing phase III studies (CODEL and CATNON) will yield critical data regarding the advisability of commonly used paradigms.

NO-96. IMMUNE-MEDIATED NEUROLOGICAL COMPLICATIONS AFTER ALLOGENEIC HEMOPOIETIC STEM CELL TRANSPLANT (AHSCT)

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Immune-mediated neurologic complications after AHSCT are rare and diagnostically challenging. Through our database, we identified 2,136 patients who underwent AHSCT between January 1992 and December 2010; 16 (median age 38, range 7-64 years; 50% men) had possible immune-mediated neurologic syndromes using diagnostic codes for demyelinating disease, multiple sclerosis, acute demyelinating encephalomyelitis (ADEM), acute inflammatory demyelinating polyneuropathy (AIDP), myelopathy, and myelitis. The cancer types were ALL (3), AML (9), CML (1), DLBCL (1), Waldenstrom macroglobulinemia (1), and MDS (1). Eleven patients received T-cell depleted peripheral blood stem cell transplant (PBSCT) or bone marrow transplant (BMT), three received unmodified PBSCT/BMT, and two received an umbilical cord stem cell transplant. Ten patients developed CNS and 6 peripheral nervous system (PNS) syndromes. The time from transplant (TT) to symptoms ranged between 4 and 1,275 days with a median of 255 days for CNS patients. Three patients developed white matter disease (WMD) on MRI and were diagnosed with ADEM, which was confirmed on brain (1) or spinal cord (1) biopsy or clinical course (1). Two patients with WMD had infectious meningoencephalitis, positive CSF CMV PCR (1), and brain biopsy with viral cytopathic effect but no specific organism (1). Two patients with abnormal T2 signal in the spinal cord and one with a normal spine MRI had myelopathy attributed to intrathecal cytarabine (2) or methotrexate (1). One patient had transverse myelitis with positive CSF PCR for EBV, and 1 had progressive brainstem WMD likely due to relapse with blasts in the CSF. PNS disease developed a median of 105 days from TT (range 69-980 days) and included AIDP (3), acute motor axonal neuropathy (2), and autonomic neuropathy (1). All patients with PNS received a trial of IVIG, two received rituximab for either EBV viremia (1) or immune-mediated neuropathy (1). Immune-related complications after AHSCT are uncommon, occur at variable time points post-transplant, and may mimic other processes such as infectious or toxic syndromes.

NO-97. INFLUENCE OF DIABETES MELLITUS TYPE II ON SURVIVAL IN GLIOBLASTOMA (GBM) PATIENTS

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INTRODUCTION: Changes in GBM treatment have resulted in prolonged overall survival. The influence of diabetes mellitus type II (DM) in GBM on survival has not yet been investigated. This study retrospectively assessed outcome in diabetic GBM patients. METHODS: All patients diagnosed with GBM and DM at MSKCC from 1/1/1998 to 1/1/2010 were reviewed. All patients had pathologically confirmed GBM. Patients were classified as diabetics when they received anti-diabetic medication >4 weeks throughout their treatment. Survival was analyzed using Kaplan-Meier. Cox regression was performed to assess for predictors of survival. RESULTS: Out of 1239 GBM patients, 124 (10%) patients (median age 67, range 29-90; median KPS 80%, range 40-100) with DM and GBM were identified. 34 (27%) cases were steroid-induced. 38 (31%) patients were women. Median HbA1c was 7.65 with a range from 5.4-13.6. Twenty-five patients (19%) were diagnosed between 1998 and 2001, 57 (47%) between 2002 and 2005, and 42 (34%) between 2005and 2009, and age, KPS, extent of resection, and treatment modalities did not significantly differ between these groups. Overall survival (OS) was 9 months (range 1-46 months) for all patients and 12 months (range 3-28 months) for patients with steroid-induced DM. Patients with steroid-induced DM who successfully tapered steroids (8/24%) had a longer OS than those who did not (17 versus 12 months). OS was 9 months in the group diagnosed 1998-2001, 12 months for 2002-2005, and 9 months for 2005-2009. On multivariate regression, age, KPS, extent of resection, RT, and successful steroid taper predicted better outcome. DISCUSSION: Diabetic GBM patients had an OS of only 9 months. Patients with steroid-induced DM survived longer, particularly if they could be tapered off steroids. Age, KPS, extent of surgical resection, and successful steroid taper were positive predictors of survival. OS for diabetic GBM patients has remained unchanged even with the introduction of new therapeutic approaches over the last decade.

NO-98. NATURAL HISTORY AND CHARACTERISTICS OF BRAINSTEM AND CEREBELLAR GLIOMAS IN ADULTS

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INTRODUCTION: Brainstem and cerebellar gliomas account for <5% of adult gliomas. The purpose of this study is to describe the natural history and clinical features of brainstem and cerebellar gliomas in adults. METHODS: We retrospectively reviewed records of adults with brainstem or cerebellar gliomas identified in the MD Anderson Cancer Center database from 1990-2010. RESULTS: We identified 153 patients with brainstem, and 82 with cerebellar glial neoplasms. Median age and KPS at diagnosis were 36 years and 90, respectively. Of the brainstem tumors, the majority were located in the pons (59%) followed by medulla (39%) and midbrain (12%) in a diffuse (61%) or focal/exophytic (37%) manner. 28% were not biopsied; in the remainder, anaplastic glioma (AG; 26%), glial tumor grade unspecified (15%), glioblastoma (13%), and juvenile pilocytic astrocytoma (JPA; 10%) were the most common histologies. Cerebellar tumors were predominantly hemispheric (54%) or vermian (39%) with the most common histologies being glioblastoma (39%), JPA (23%), and AG (20%). Oligodendrogliomas were rare and accounted for less than 2% of all brainstem and cerebellar gliomas. Patients with cerebellar gliomas had a better median overall survival (46.3 months) compared to those with brainstem gliomas (34.5 months; $p = 0.06$). Patients with JPA had the best prognosis regardless of location. Among brainstem tumors, focal/exophytic tumors had a significantly better median survival (51.3 months) than diffuse tumors (20.9 months; $p = 0.01$). Additionally, survival was poorest for patients with glioblastoma (12.1 months) and best for those with grade unspecified (90.3 months). Among cerebellar gliomas, patients with AG had a better median survival (19.7 months) than those with glioblastoma (13.6 months). CONCLUSIONS: In this large series, we describe the localization and histology of brainstem and cerebellar gliomas in adults and the relevance to outcome. Survival was similar for brainstem and cerebellar high-grade gliomas. Adults with diffuse brainstem gliomas have better survival than pediatric patients.

NO-99. ELEVATED GLUCOSE LEVELS AND SURVIVAL IN ELDERLY PATIENTS WITH NEWLY DIAGNOSED GLIOBLASTOMA

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INTRODUCTION: Hyperglycemia has been associated with poor outcomes in many disease states including cancer. Hyperglycemia augments in vitro astrocytoma cell growth. We undertook this study to evaluate the relationship between preoperative glucose levels and survival in elderly patients with newly diagnosed glioblastoma (GBM). METHODS: With IRB approval, the Cleveland Clinic Brain Tumor and Neuro-Oncology Center's database was used to identify patients ≥65 years old at diagnosis with histologically confirmed GBM. Patients with known diabetes and those in whom preoperative glucose was not available within 30 days prior to surgery were excluded from the analysis. The analysis was based on a recursive partitioning algorithm that included preoperative glucose, Karnofsky performance scale score (KPS) and patient age because these are recognized prognostic factors. RESULTS: 242 GBM patients with a

median age of 74 (range 65-91, 52% male) were included. 32% of patients underwent gross total resection, 6% had near total resection, 19% had subtotal resection, and 43% had biopsy only. Following surgery, 74% of patients underwent radiation, and 43% received chemotherapy. Median preoperative glucose was 123 mg/dL (range 69-306). Median overall survival was 5.2 months (95% C.I. 4.7-6.6 months). Patients were divided into 4 groups: group one (KPS $>$ 70, age $<$ 75 and preoperative glucose $<$90 mg/dL), group two (KPS $>$70, age $<$75, and preoperative glucose $>$90 mg/dL), group three (KPS $>$ 70, age $>$ 75, any glucose level), and group four (KPS $<$ 70, any age, any glucose level). Median survival times for patients in groups one, two, three, and four were 14.0, 7.9, 5.1, and 3.0 months, respectively. Compared with patients in the favorable group (group one), those in groups two, three, and four were at progressively higher risk of dying (P $<$0.001). CONCLUSION: Higher preoperative glucose level is associated with decreased overall survival in elderly GBM patients. Strict glucose control may contribute to improved outcome in treatment of these patients.

NO-100. KNOW THY ENEMY: PARADOXES TO BE EXPLOITED IN GLIOBLASTOMA

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In the past 50 years, virtually no progress has been made in understanding the biology and treatment of glioblastoma, and the median prognosis has not changed significantly. For the first time, we may have a useful tool in the war against glioblastoma. We have observed paradoxes in tumor growth and response to therapy that we believe can be exploited and used against the tumor enemy. Using a patient-specific mathematical model for glioblastoma growth and invasion, we have calculated the growth rates of 35 glioblastomas and revealed that although about two-thirds of the patients have survived relatively long times, only about half of these can be attributed to their treatments. In other words, the other half of the long-surviving patient population has not survived longer than would be predicted from their rates of growth if not treated. This contradiction is due to two paradoxes in their responses to treatment: 1) patients with some of the most rapidly growing glioblastomas benefit the most but still survive only slightly longer than the average, and 2) patients with some of the most slowly growing glioblastomas benefit the least but still survive longer than the average. These interpretations are possible only because the growth rates have been measured in the 35 patients and are impossible to reach in other patients whose growth rates have not measured. The biological hypothesis that radiotherapy and chemotherapy are directed at mitotic activity fits with these observations. These paradoxes suggest that the treatment of glioblastomas as a single homogeneous group without respect to rates of growth or invasion should obviously be reconsidered as leading much too slowly to any significant progress in conquering such a heterogeneous enemy.

NO-101. SILENT CORTIOTROPH ADENOMAS, A COMPARISON WITH NON-FUNCTIONAL ADENOMAS

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BACKGROUND: Silent corticotroph adenomas (SCAs) represent a distinct pathological entity of non-functional adenomas (NFAs) with some literature suggesting a distinct clinical behavior and recurrence potential. METHODS: We conducted a retrospective review of all SCAs at our institution over the last 10 years. Clinical, radiological, and pathological features were reviewed. The series was compared to a matched cohort of NFAs. Statistical analysis was carried out to detect statistically significant trends. Results were compared to the literature. RESULTS: Twenty patients had SCAs. Four were treated recently and had a very short followup. Sixteen patients were included in the final analysis. Nine patients (56%) were female. Mean age was 52 years (range 24-78 years). Six patients (38%) had visual compromise on presentation. Two patients (12.5%) presented with acromegaly secondary to double adenoma (1 silent corticotroph and 1 somatotroph adenoma). Two patients presented with apoplexy. Two patients presented with secondary amenorrhea. Two tumors were incidental findings. One patient presented with headache and 1 patient presented with symptoms related to cavernous sinus (CS) invasion. All the tumors were macroadenomas, and five of them (29%) had frank CS invasion. Three tumors showed evidence of a hemorrhage (2 presented with apoplexy and 1 presented with visual deficit after a hemorrhage in a tumor cyst). Gross total resection was achieved in 8 cases (50%). Two tumors (12.5%) recurred over a mean follow up period of 36 months. Compared to NFAs, SCAs were more likely to bleed (p-value 0.014), have double adenoma (p-value 0.047), and have less expression of FGFR4 (p-value 0.007). There was no difference in recurrence rate between SCAs and NFAs (p-value 0.8). CONCLUSION: SCAs are more likely to have invasive presentation. Over the followup period in our series, risk of recurrence in the SCA group did not increase compared to the NFA group. Postoperative radiation should be reserved for tumors with evidence of recurrence.

NO-102. PHASE II TRIAL OF DASATINIB IN TARGET SELECTED PATIENTS WITH RECURRENT GLIOBLASTOMA (RTOG 0627)

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BACKGROUND: Glioblastoma (GBM) has a poor prognosis after recurrence. Dasatinib is a multi-targeted tyrosine kinase inhibitor with at least 4 targets potentially important in GBM biology: SRC, c-KIT, EPHA2, and PDGFR. We conducted a phase II trial of dasatinib at 100 mg bid for patients with recurrent GBM. METHODS: Eligibility required KPS $\geq$ 60; age $\geq$ 18; no current treatment with H2-blockers, proton pump inhibitors, EIAEDs, antiplatelet agents, or anticoagulants; prior treatment with radiotherapy and temozolomide only; and activation/overexpression by immunohistochemistry of at least 2 of the above 4 dasatinib targets in archival tumor tissue. Efficacy was measured by objective radiographic response or 6 month progression free survival (6mPFS). Using a 2-stage design, 55 eligible patients were needed to detect an absolute improvement of 14% to 25% over a historical baseline of 11%. RESULTS: Interim analysis of stage 1 (n = 29) suggested efficacy. Because treatment-related toxicity was infrequent at 100 mg bid, stage 1B allowed intrapatient dosage escalation by 50 mg daily every cycle as tolerated (maximum 200 mg bid). Escalation was tolerable in 10/17 patients, but there were no responses, and 6mPFS was achieved in only in 2/31 (6%) patients. Among eligible patients (stages 1 and 1B, n = 52), the median PFS was 1.7 months, OS 7.5 months, and 6mPFS rate $<$ 10% with no responses. The clinical benefit rate was too low to correlate tumor phenotype with activity. The trial was closed without proceeding to stage 2. CONCLUSION: Dasatinib as monotherapy is not effective in recurrent GBM, despite higher doses. Intrapatient dose escalation of dasatinib was feasible in most patients; therefore, future trials of dasatinib in combination regimens for GBM may be able to use higher doses than the usual monotherapy dose.

NO-103. PARTIAL RESOLUTION OF PULMONARY METASTASES FROM MENINGIOMA TREATED WITH BEVACIZUMAB: A CASE REPORT

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INTRODUCTION: Meningiomas are the most common primary brain tumor in adults, accounting for 20% of all intracranial tumors, and have a 10-year recurrence rate of 20-50% despite treatments that include aggressive surgery and irradiation. Treatment options for unresectable or refractory meningiomas (chemotherapy and hormonal therapy) have been generally ineffective. Bevacizumab, a vascular endothelial growth factor receptor inhibitor, has been recently reported to have activity in these unresectable and refractory tumors (Puchner *et al. Ann Oncol*. 2010;21(12):2445). We report a case of a 41-year-old male with recurrent meningioma and pulmonary and metastases who achieved a partial response with bevacizumab. RESULTS: In 2007, a 41-year-old man presented with headaches, and he was found to have multifocal intracranial mass lesions by magnetic resonance imaging (MRI) evaluation. He underwent bifrontal craniotomy for resection of frontal and occipital meningiomas. In November 2009, he again developed headaches, and at that time, a brain MRI revealed at least three new lesions. Surgery was proposed. A preoperative chest x-ray showed evidence of bilateral metastatic lesions, and a lung biopsy revealed metastatic meningioma. In February 2010, the patient underwent gamma-knife radiosurgery. From April 2010 until August 2010, the patient received 8 cycles of bevacizumab 10 mg/kg every two weeks. No toxicity from

bevacizumab was observed. A followup computed tomography (CT) scan of the chest in August 2010 showed that the pulmonary index lesion had significantly decreased in size (4.6 cm x 2.9 cm to 3.0 cm x 1.9 cm), and the remaining pulmonary lesions demonstrated a 1-2 mm decrease in size. In December 2010, a CT scan showed a marked increase in the size of the lung metastases. CONCLUSION: Bevacizumab may have an important therapeutic role in the treatment of unresectable or refractory meningiomas and should be evaluated further.

NO-104. TREATMENT OF PRIMARY CNS LYMPHOMA: COMPARISON OF TWO HIGH-DOSE METHOTREXATE-BASED CHEMOTHERAPY REGIMENS

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Even though there is some convincing data that high-dose methotrexate-based chemotherapy regimens improve survival compared to previous controls treated with radiotherapy alone, the optimal treatment approach is still unclear. We retrospectively analyzed 31 primary CNS lymphoma (PCNSL) patients (25 men and 6 women) from January 2003 to March 2008. Nineteen patients (median age 55) received 2 courses of vincristine, methotrexate (MTX), and procarbazine (HD MVP regimen) every 4 weeks. Twelve patients (median age 50) received 1 cycle of cyclophosphamide, doxorubicin, vincristine, and dexamethasone and 2 cycles of carmustine, vincristine, cytarabine (CHOD-BVAM) every 6 weeks. Overall response rates to treatment were as follows: complete remission in 9/19 (47.4%) patients in the HD MVP group and 6/12 (50.0%) in the CHOD-BVAM group; partial remission in 7/19 (36.8%) HD MVP patients and 1/12(8.3%) CHOD-BVAM patients; and early death during chemotherapy in 3/19 (15.8%) HD MVP patients and 5/12 (41.7%) CHOD-BVAM patients. There were 3 patients with progression and 2 with relapse after treatment in HD MVP group and 3 relapses after treatment in CHOD-BVAM group. Grade 3 and higher hematological complications were significantly more common in the CHOD-BVAM group. Four-year actuarial overall survival rate was 40%. High-dose methotrexate in combination with other active chemotherapy agents with or without radiation therapy is effective to treat PCNS lymphoma. With current treatment regimens, long-term survival is possible for PCNS lymphoma patients less than 60 years of age with good performance (ECOG 1) at presentation. Because of the relatively lower incidence of severe hematologic complications, HD MVP (without intrathecal MTX & HD AraC) with or without radiation therapy could be a reasonable and relatively safe treatment option for PCNSL.

NO-105. CYSTIC GLIOMAS ARE QUANTITATIVELY LESS BIOLOGICALLY AGGRESSIVE

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Gliomas are primary brain tumors with varying degrees of biological aggressiveness that invade normal brain tissue on a cellular level, which hinders treatment effectiveness. A subset of these lesions develops fluid-filled cysts. A recent study of 22 patients suggests that cysts in glioblastomas (GBMs) incur a significant survival advantage for these patients (Maldaun, J Neurosurg 2004). We have observed a statistically significant survival advantage for cystic glioma patients ($N = 32$) compared to our age-matched control patient population ($N = 44$, $p = 0.0139$, Student's t-test), a result that was independent of any difference in age between the groups ($p = 0.1018$, Student's t-test). We hypothesize that these two types of tumors must have different growth dynamics that lead to different prognoses for the same disease. Our patient-specific mathematical model for glioma kinetics extracts rates of net proliferation (ρ), net diffusion rate (D), and velocity of radial tumor growth from pre-treatment MRIs (T1Gd and T2). Because cyst fluid is not composed of proliferating tumor cells, we utilized a novel approach of cyst exclusion from one or both MRI modalities to allow estimation of the model parameters and tumor growth velocity. Cystic gliomas were found to have a statistically lower ratio of proliferation to invasion (ρ/D) a previously confirmed indicator of tumor aggressiveness (Szeto, 2009). Although there was significant overlap in the distribution of survival times between the cystic and noncystic glioma groups, there were several very long-lived patients with cystic disease. Amongst patients with cystic gliomas, those with the most favorable survival (>900 days) had a relatively small (<15%) cystic volume when compared with the overall T2 imageable volume ($p = 0.0290$, Fisher exact test). These findings suggest a kinetic basis for the more favorable prognosis for cystic tumors, the most benign of which have small cysts compared to their overall tumor burden.

NO-106. BCNU IMPREGNATED WAFER (GLIADEL) CHEMOTHERAPY-INDUCED BONE AND SCALP SARCOMA

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INTRODUCTION: Glioblastoma multiforme (GBM) has poor prognosis after recurrence. Treatment is challenging because chemotherapy does not penetrate the blood-brain barrier. Over the course of 3 weeks, 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU)-impregnated wafers provide a controlled release of local high-dose chemotherapy to the resection cavity within one centimeter of the resection margins and minimize the systemic effects of chemotherapy. The described side-effects of the BCNU wafer include cerebral edema and pericavity necrosis, but no report of secondary malignancies caused by the high-dose BCNU wafers and their potential for mutagenesis has been printed to date. METHODS: We present the case of a 53-year-old woman with GBM who developed a secondary malignancy after the placement of BCNU wafers. This patient underwent gross total resection with craniectomy followed by radiation and chemotherapy with temozolomide without a bone flap in place. Subsequently, the patient underwent a second gross total resection of her GBM with reinstallation of her previously stored bone flap and BCNU wafer placement. One year after the surgery, the patient developed a rapidly enlarging scalp mass near the posterior aspect of her incision. She underwent gross total resection of her scalp mass and the underlying bone with an extensive plastic reconstruction. RESULTS: Head CT at the time of scalp mass presentation showed that her craniotomy flap was partially eroded by a soft tissue mass. Brain MRI showed a mass extending from the bone flap and into the epidural space contiguous with the dura near the sagittal sinus. The pathology showed undifferentiated sarcoma. Brain MRI one month after resection showed recurrence of the tumor in the occipital area. CONCLUSION: The most common complications of BCNU wafers are malignant cerebral edema, cyst formation in the resection cavity, cerebrospinal fluid leak, wound healing abnormalities, and increased perioperative seizure activity. Here we present the first case report of BCNU chemotherapy wafers-induced undifferentiated sarcoma.

NO-107. 45-YEAR-OLD MAN WITH NEWLY DIAGNOSED MEDULLOBLASTOMA TREATED WITH TEMOZOLAMIDE

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Medulloblastoma is a malignant CNS tumor that occurs primarily during childhood. It constitutes only 1% of all intracranial tumors in the adults. Because of its relative infrequency in older patients, the clinical characteristics of this disease are less well defined in adults than in children, and an optimal treatment regimen is not yet established. Complete tumor resection with craniospinal radiation is the standard of care for treatment of adult medulloblastoma. In contrast to childhood medulloblastoma, the role of chemotherapy in adult disease is undetermined. Some chemotherapy regimens used for the pediatric population have been evaluated and used, including vincristine, CCNU, cisplatin, carboplatin, and cyclophosphamide. We report a case of 45-year-old man diagnosed with medulloblastoma in the cerebellum in 2006 who subsequently underwent total surgical resection followed by radiation therapy. After an extensive discussion, he was started on temozolomide 150 mg/m2, 5 days on, 23 days off, for 24 cycles of chemotherapy over a period of 2 years with minimal toxicity. He was followed with serial MRI of the brain without any evidence of recurrent disease, which currently makes our patient recurrence-free for 4.5 years. Temozolomide is a second-generation cytotoxic alkylating agent that shows a favorable penetration in the CNS and has yielded promising results in the treatment of gliomas. Very few cases of adults medulloblastoma treated with temozolomide have been reported. Our case shows the antitumor effect of temozolomide in the treatment of medulloblastoma with minimal toxicity. Most of the data in the literature are based on retrospective analysis rather than randomized studies because of the small number of adult patients with this disease. The optimal treatment regimen is not yet established for this tumor, and because of its rarity, cooperative multi-institutional clinical trials will be required to define the best treatment.

NO-108. A PHASE II TRIAL EVALUATING THE EFFECTS OF BORTEZOMIB IN PATIENTS WITH RECURRENT MALIGNANT GLIOMAS TREATED PRIOR TO SURGERY AND THEN BORTEZOMIB AND TEMOZOLOMIDE POSTOPERATIVELY

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BACKGROUND: NF-Kappa B is one of the mechanisms of resistance for malignant gliomas. A few trials have assessed bortezomib in the treatment of malignant gliomas with limited activity. This may be due in part to limitations in dose escalation caused by peripheral neuropathy. We performed a phase II trial with the goal of measuring bortezomib in tumor tissue and its effects on NF-Kappa B. METHODS: Patients thought to be surgical candidates were enrolled after signing an IRB-approved consent form. They were treated with bortezomib 1.7 mg/m2 IV on day 1, 4, and 8 and then had surgery on day 8 or 9. Approximately 14 days postoperatively, patients were started on temozolomide 75 mg/m2 PO on days 1-7 and 14-21; on days 7 and 21, they received bortezomib 1.7 mg/m2 (1 cycle was 1 month). Treatment continued until progression. If <1 patient had PFS at 6 months, the trial would be stopped. RESULTS: 10 patients were enrolled (8 men and 2 women). Median age and KPS were 50 years (range 42-64) and 90% (range 70%-90%), respectively. Only 1 patient could not go on to surgery because of an intracranial hemorrhage and clinical deterioration. The median number of postoperative treatment cycles was 2 (range 1-4), with two patients removed from the study: one for infection (after 3 cycles, not restarted due to prolonged delays) and one for meningitis (after 2 cycles, withdrew from the trial). Six patients are deceased. The trial was stopped because no patient had a 6 month PFS. Tissue samples are currently being subjected to PK and NF-Kappa B analysis. CONCLUSION: Postoperative treatment with temozolomide and bortezomib did not have any activity in recurrent malignant gliomas. Tissue analysis is underway to determine if this is because of a lack of drug penetration or inability to inhibit NK-Kappa B sufficiently.

NO-109. AGGRESSIVE TREATMENT OF ATYPICAL/ ANAPLASTIC MENINGIOMA

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Atypical Grade II meningiomas comprise 20 to 35% of all meningiomas, and the 5-year survival rate has been reported to range from 28% to 61%. Anaplastic meningiomas, Grade III, comprise about 5 to 10% of these tumors and have an even poorer prognosis. There is no accepted method of treatment, and no chemotherapy has been found to be efficacious. Two cases of anaplastic meningioma and one of atypical meningioma are presented. Case #1 is a 64 year old female who underwent resection of a right frontal-parietal atypical meningioma that recurred 3 months later. She then underwent intensity modulated radiotherapy (IMRT) and adjuvant temozolomide for one year with no further recurrence after 76 months. Case # 2 is a 55 year old female who underwent resection of an anaplastic meningioma that recurred one month later. She also underwent treatment with IMRT and adjuvant temozolomide for one year and has no further recurrence after 63 months. Case # 3 developed a malignant transformation of a benign meningioma diagnosed 14 years earlier. Resection verified atypical meningioma, which was treated with IMRT and temozolomide and recurred 3 months later as a systemic anaplastic meningioma. There was no brain recurrence for 11 months. The patient's survival after diagnosis of atypical pathology was 13 months, and death was due to widespread systemic disease. Improved treatments are needed for this aggressive type of tumor. Temozolomide and radiotherapy may be a reasonable protocol, especially when used early in the treatment phase, and it is well tolerated.

NO-110. INTRATUMORAL CONCENTRATIONS OF SUNITINIB AFTER ORAL ADMINISTRATION IN PATIENTS WITH HIGH GRADE GLIOMA

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INTRODUCTION: Sunitinib is an oral tyrosine kinase inhibitor of VEGFR1, VEGFR2, VEGFR3, PDGF receptor, c-KIT, and FLT-3 and is currently in clinical trials to assess its efficacy in malignant gliomas. In vivo studies of mice implanted with U87MG human glioma cells suggest that sunitinib achieves high concentrations in brain tumors. However, the penetration of sunitinib into high-grade gliomas in humans has not been determined. METHODS: Eight patients with progressive high-grade glioma for whom repeat surgical tumor debulking was clinically indicated after prior chemoradiation received sunitinib for 7 days prior to surgery (150 mg on day 1 and 50 mg on days 2-7). Patients resumed sunitinib treatment 14 days after surgery (50 mg daily on 4/2 weekly schedule) and continued treatment until disease progression or unacceptable toxicity. Tumor samples were collected during surgery, and plasma samples were obtained immediately before and after resection. The concentration of sunitinib in the plasma and tumor samples was determined using high performance liquid chromatography with mass spectrometric detection. RESULTS: The median patient age was 53 years, and 75% of patients were men. One patient experienced perioperative stroke and wound infection. Recurrent glioma was noted in all but 1 sample, which was found to contain necrosis and treatment effect. This sample was excluded from pharmacokinetic analysis. The median concentration of sunitinib was 180.0 ng/g (range 55.5-911.8 ng/g) in the 7 tumor specimens and was 60.9 ng/ml (range 32.5 - 96.2) in the paired blood samples. The median tumor-to-plasma ratio was 3.1 (range 1.0-20.5). Median time to progression on sunitinib was 72 days (range 17 to 199 days). CONCLUSIONS: These findings suggest that sunitinib achieves intratumoral concentrations higher than in plasma and penetrates the blood-brain barrier in high-grade gliomas. Tumor specimens are being analyzed separately to determine the phosphorylation status of VEGFR2 and PDGF-Beta receptor.

NO-111. TREATMENT OF CEREBRAL RADIATION NECROSIS WITH BEVACIZUMAB: THE CLEVELAND CLINIC EXPERIENCE

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BACKGROUND: Radiation necrosis is a serious complication of radiation treatment for brain tumors. Therapeutic options including steroids, anticoagulation, and hyperbaric oxygen have limited efficacy. Radiation necrosis is postulated to be a continuous process involving endothelial cell dysfunction that leads to tissue hypoxia and necrosis with secretion of the vascular endothelial growth factor (VEGF). Bevacizumab, an antibody against VEGF, has been reported to reduce edema in patients with suspected radiation necrosis. METHODS: After obtaining IRB approval, we used the Cleveland Clinic Brain Tumor and Neuro-Oncology Center's database to identify patients who were treated with bevacizumab between 7/2007 and 1/2011 for radiation necrosis diagnosed on the basis of magnetic resonance imaging (MRI) and/or biopsy. RESULTS: 11 patients with a diagnosis of radiation necrosis (4 were biopsy proven) received bevacizumab. Post-treatment MRI was performed at an average of 8 weeks after initiating therapy with bevacizumab. Follow-up MRI demonstrated a radiographic response in all patients on the MRI fluid-attenuated inversion-recovery (FLAIR) sequences, and 10 of 11 patients showed improvement in the T1-weighted post-gadolinium contrast images. The average area change in the T1-weighted post-gadolinium contrast abnormalities was 53.7%, and the average change in the FLAIR images was 65% (using McDonald's criteria). Ten patients showed clinical benefit. There was a mean daily dose reduction of 6.2mg of dexamethasone after initiation of bevacizumab. CONCLUSIONS: Bevacizumab therapy appears to produce radiographic response as well as clinical benefit for patients with cerebral radiation necrosis.

NO-112. PATIENT-SPECIFIC MATHEMATICAL RADIATION ONCOLOGY: 4D OPTIMIZED DOSE DISTRIBUTIONS INFORMED BY GLIOMA KINETICS OF PROLIFERATION AND INVASION

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A standard clinical radiation treatment for a glioblastoma consists of 60 Gy delivered on weekdays over 6 weeks (2 Gy per treatment day). Typically, radiation is applied to the T2 abnormality plus a 2 cm margin for 25 days followed by a "boost" dose to the T1 abnormality plus a 2 cm margin for 5 to 8 days. This one-size-fits-all approach does not explicitly account for tumor growth kinetics or the extent of hypoxia, which leads us to believe that the uniform doses applied in standard clinical treatments are suboptimal. A patient-specific mathematical model of glioblastoma utilizing the standard L-Q model [Rockne 2010] has been shown to predict untreated spatiotemporal proliferation and invasion of the tumor as well as the effect of clinical radiation therapy. We integrated this model with a multiobjective evolutionary algorithm that optimizes weekly dose distributions to maximize tumor cell killing [Holdsworth 2011]. Using the integrated model, simulated results demonstrate that the individualized plans optimized for tumor-specific biology can be much more effective in curbing tumor growth than current clinical treatment protocols while maintaining the same dose to normal tissue. Simulations for 3 patients with individualized dose distributions showed significantly different levels of effectiveness for individualized radiation treatments depending on the degree of radiosensitivity of the tumor. For highly radiosensitive tumors, a 50% increase in cell death was observed, whereas for radioresistant

tumors, the cell death was roughly the same. These results suggest that a patient-individualized approach to radiation treatment design could be beneficial in some patients suffering from this uniformly fatal disease and support the integration of such approaches into clinical trials for validation.

NO-113. SEQUENTIAL TREATMENT WITH TEMOZOLOMIDE, PCV, AND RADIATION FOR GRADE II OLIGODENDROGLIOMAS

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INTRODUCTION: The optimal treatment for low grade oligodendrogliomas (LGO) is unknown, but radiation therapy (RT), temozolomide (Tmz) and combination chemotherapy with PCV have shown efficacy. Most patients with LGO have prolonged survival and eventually receive multiple treatments. METHODS: We retrospectively assessed clinical course and outcomes in patients initially diagnosed with LGO who received both Tmz and PCV at any point. RESULTS: 25 patients were identified. Pure LGO histology was found in 19 (1p was deleted in 9, intact in 3, and its status unknown in 7) and mixed oligoastrocytoma in 6 (1p deleted in 3, and its status unknown in 3) patients. The median age at diagnosis was 34; 14 patients were women. Treatment at initial diagnosis was given in 5 patients (4 RT, 1 PCV). Median time to first treatment was 29 months (range 0-173 months). Median time to second treatment was 99 months (range 16-210 months). 21 patients also received RT at some point. Median overall survival was 147 months (range 67-340 months) with 9 patients still alive at last follow up (median 192 months, range 141-340). There was a clear trend for decreased progression free survival after subsequent treatments. There was a trend for longer progression free survival (median 81 months) before second treatment in those initially treated with PCV compared to Tmz (57 months) and RT (65 months), but this did not reach statistical significance. Some partial responses to second or third treatments were observed in all groups: 1 patient received PCV after Tmz; 3 PCV after RT; 3 Tmz after PCV; 3 RT after PCV. By Kaplan-Meier analysis with censoring, there was no significant difference in overall survival between patients initially treated with PCV versus those treated with Tmz or RT, although the numbers were small. Conclusions are limited by the retrospective, uncontrolled nature of the study and small numbers of patients.

NO-114. PREDICTIVE INTEGRATION OF TUMOR GROWTH KINETICS ON CLINICAL IMAGING WITH HISTOLOGICAL FEATURES THROUGH PATIENT-SPECIFIC SIMULATION

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INTRODUCTION: Gliomas are heterogeneous primary brain neoplasms that can progress from low-grade to high-grade (glioblastoma). Although low-grade gliomas involve low degrees of angiogenesis, glioblastomas are considered highly angiogenic. This suggests that interactions between glioma cells and the tumor microenvironment play an important role in aggressive tumor formation and progression. The dynamics of these interactions connecting tumor growth rates and histological features are not well explored in individual patients. Using a mathematical model, we have successfully integrated clinical imaging and histopathology to predict imaging and histological features on a patient-specific basis. METHODS: To quantitatively explore tumor-microenvironment interactions, we modeled the interactions of normoxic glioma cells, hypoxic glioma cells, vascular endothelial cells, diffusible angiogenic factors, and necrotic activity, all hallmarks of the histological diagnosis of glioma. Patient-specific model parameters were computed from pretreatment magnetic-resonance imaging (MRI) and used to calibrate the model. Patient-specific simulations integrated multi-modality imaging with histopathology for 8 glioblastoma patients. Model-simulated predictions were compared to histologic tests including WHO grade, Ki67 proliferation index, mitotic activity, and HIF1alpha ALLRED score as well as the size of the necrosis and contrast-enhancing volume on MRI. RESULTS: Model simulations quantitatively predicted the spectrum of in vivo dynamics of gliomas visualized with medical imaging for features that characterize increasing degrees of "malignancy," which include the degree of cellularity, mitoses, hypoxia-induced neo-angiogenesis, and necrosis. Model predictions of 7 histological and imaging features across 8 patients fell within 3 standard deviations of the mean for a preponderance of those tested. This indicated that the model is capable of integrating tumor kinetics and histology across a wide range of tissue and imaging scale heterogeneity. This provides a novel tool for bridging macroscopic measures of tumor growth with microenvironmentally-driven histological features in individual patients, thus providing unique predictive insight into each patient's tumor through an in silico virtual control.

NO-115. PACLITAXEL POLIGLUMEX (PPX), TEMOZOLAMIDE (TMZ) AND RADIATION (RT) FOR NEWLY DIAGNOSED HIGH-GRADE GLIOMAS: A BROWN UNIVERSITY ONCOLOGY GROUP (BRUOG) PHASE II STUDY

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BACKGROUND: Paclitaxel poliglumex (PPX) is drug conjugate that links paclitaxel to a polyglutamic acid polymer, which results in an increased radiation enhancement factor. Phase I/II studies of PPX in esophageal cancer established a dose of 50 mg/m^2/week with concurrent chemotherapy/radiotherapy (RT). The primary objective of this study is to determine the safety of PPX with standard temozolomide (TMZ) and RT for high-grade gliomas. METHODS: Patients received weekly PPX 50 mg/ m^2 and daily TMZ 75 mg/m^2 for 6 weeks with concomitant RT (60 Gy). Adjuvant chemotherapy with TMZ (200 mg/m^2/d x 5 d) every 28 days was started 1 month after completion of chemoradiation. RESULTS: This study completed its planned accrual of 25 patients (median age, 60 years; 48% male; 60% GBMs). Grade 4 hematologic toxicity occurred in 6 of 25 patients, started 4-6 weeks after initiating PPX with TMZ and RT, and lasted up to 5 months. Median follow-up was 18.75 months (range, 1-26.75). The median PFS was 16.25 months for all patients and 13.5 months for the GBM patients. Of 16 patients with post-PPX enhancement, 13 had pseudoprogression, and initial rCBVs ranged from 0.63 to 6.25 (mean 2.43), but rCBVs subsequently stabilized or monotonically decreased. Two patients with pseudoprogression later had progressive disease (mean time to progression = 105 days; rCBVs at progression were 2.72 and 4.09, mean = 3.41). rCBV in progressive disease was not significantly larger than the initial rCBV in pseudoprogression ($p = 0.44$, unpaired t-test). Five of the patients with pseudoprogression had resection (2) or biopsy (3). Pathologic specimens showed gliotic edematous brain, and all had Ki-67 < 5%. CONCLUSIONS: PPX is a promising radiation enhancer in high-grade gliomas. Stable or decreasing rCBV on longitudinal follow-up exams may provide a better indication of pseudoprogression than individual absolute rCBV values. Hematologic toxicity may be due to interaction between PPX and TMZ. Results will be updated.

NO-116. HEARING AND RADIOGRAPHIC RESPONSE OF NEUROFIBROMATOSIS 2-RELATED VESTIBULAR SCHWANNOMA TO BEVACIZUMAB: A RETROSPECTIVE REVIEW OF 31 PATIENTS

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BACKGROUND: Early studies suggest that bevacizumab treatment results in hearing improvement in neurofibromatosis 2 (NF2) patients who have progressive vestibular schwannomas in their only hearing ear. We now report a longer follow-up in a larger cohort of similar patients. METHODS: We studied 31 consecutive NF2 patients who received bevacizumab for progressive vestibular schwannomas at our center. Hearing was assessed using audiometry, and tumor size was measured using volumetric MRI. A hearing response (or loss) was defined as an improvement (or decrease) in word recognition score above the 95th percentile confidence interval compared with baseline; a radiographic response (or progression) was defined as a $\geq$ 20% decrease (or increase) in tumor volume compared with baseline. RESULTS: The median patient age was 26 years (range, 12 - 73 years), and 45% of patients were male. The median volumetric tumor growth rate before starting treatment was 70% per year. At the time of analysis, the median duration of treatment was 14 months (range, 6 - 41 months). A hearing response occurred in 13/23 (57%) evaluable patients and a radiographic response in 17/31 (55%) of evaluable patients. The median time to response was 3 months for both endpoints. 88% of patients had stable or decreased tumor size after 1 year of treatment, 67% at 2 years, and 54% at 3 years. 90% of patients had stable or improved hearing after 1 year of treatment, 81% at 2 years, and 61% at 3 years. Overall, treatment was well tolerated. Of the 168 adverse events observed during 572 patient-months of follow-up, 133 (79%) were grade 1, 26 (15%) were grade 2, 8 (5%) were grade 3, and 1 (1%) was grade 4. CONCLUSION: Bevacizumab treatment was followed by hearing improvement and tumor shrinkage in over 50% of NF2 patients with progressive vestibular schwannomas, and stable or improved hearing was retained in the majority of patients.

NO-117. THE CLINICAL APPLICATION OF 2-HYDROXYGLUTARATE (2HG) IN THE MANAGEMENT OF IDH-MUTATED GLIOMAS

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Isocitrate dehydrogenase converts isocitrate to alpha-ketoglutarate (alphaKG) in the cytosol (IDH1) and mitochondria (IDH2). The identification of mutations in IDH1 and IDH2 among the majority of patients with WHO grade II and III gliomas has directed attention to the role of abnormal metabolism in the pathogenesis and progression of these tumors. The mutations are confined to the active site of the enzyme and result in a gain of function that causes the mutant enzyme to produce D-2-hydroxyglutarate (2HG). This metabolite, normally present in vanishingly small quantities, can be elevated by orders of magnitude in gliomas harboring IDH1 or IDH2 mutations. Although the metabolic consequences and downstream molecular effects of these mutations have yet to be elucidated, their potential value as diagnostic and prognostic markers in gliomas has been established from their clear association with improved overall survival when outcomes are compared between IDH-mutant and IDH wild-type tumors. We have an enrolling IRB-approved clinical protocol to develop magnetic resonance spectroscopy (MRS) at 3Tesla for low abundant metabolites in patients with gliomas. Using optimized point-resolved spectroscopy (PRESS) and difference editing sequences, we have detected 2HG *in vivo* by MRS. When our technique was applied to tumors in 30 patients with all grades of malignant gliomas, we achieved 100% sensitivity and specificity. For each case in which 2HG was detected by MRS, an IDH1 or 2 mutation in the tumor was confirmed by DNA sequencing. Failure to detect 2HG by MRS was associated with the detection of wild type IDH1 and 2 in each case. Data will be presented showing the sensitivity of 2HG in detecting tumor progression and correlating 2HG levels with response to treatment. The ease with which 2HG measurement could be incorporated into standard MR imaging suggests that it may be an important biomarker in the clinical management of IDH mutated gliomas.

NO-118. TREATMENT OF PINEAL GLIOBLASTOMA WITH LEPTO MENINGEAL METASTASES- CASE REPORT

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Glioblastoma multiforme (GBM) is the most common primary malignancy of the central nervous system. Pineal GBM is an exceedingly rare tumor with very poor prognosis. Only 18 cases so far have been reported in the literature. We present a case of pineal gland GBM with leptomeningeal disease successfully treated with chemotherapy and radiation. A 55 year old man presented with progressive headache and Parinaud syndrome. Brain MRI showed an enhancing pineal mass with hydrocephalus. The patient had a biopsy done along with a ventriculo-peritoneal shunt placement. The pathology was consistent with GBM with a Ki-67 labeling index of 30-50%.The patient was readmitted within 2 weeks of biopsy with worsening of Parinaud syndrome and the development of peduncular hallucination. Repeat brain and total spine MRI showed an increase in the size of the pineal lesion (measuring 2.6 X 2.5 X 2.8 cm) and diffuse linear leptomeningeal disease. Chemotherapy with temozolomide at 150mg/m2 was started. On day 3 of temozolomide treatment, the patient developed cauda equina syndrome. High-volume lumbar puncture was performed, and he received one dose of 10 mg intrathecal methotrexate. Within 24 hours following the methotrexate treatment, the patient showed significant improvement of the cauda equina syndrome. Initial lumbar puncture showed a markedly elevated protein count of 2856, cytology was negative, and WBC counts were within normal limits. High-volume lumbar puncture was repeated with intrathecal methotrexate two days apart. Two weeks of hypofractionated radiation therapy to the pineal lesion with concurrent temodar was given. The patient had significant improvement of peduncular hallucinations and Parinaud syndrome after the radiation. He was further treated with avastin every 2 weeks and monthly temozolomide (5/23). The followup brain MRI after two months of treatment showed that his pineal mass size has decreased to 1 X 1.5 X 1.2 cm, and his CSF protein level has improved to 315.

NO-119. UTILITY OF CEREBROSPINAL FLUID CYTOLOGY IN THE DIAGNOSIS OF NEOPLASTIC MENINGITIS

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BACKGROUND: Cerebrospinal fluid (CSF) is a valuable diagnostic tool in patients with cancer. However, this test is of limited utility when not guided by clinical judgment. METHODS: Retrospective analysis of CSF cytology for detection of carcinomatous meningitis was performed. The determination of the utility CSF cytology was based on a previously determined clinically significant difference between the pretest probability of disease and the post-test probability. Patients without cancer ($n = 403$), patients with known cancer without suspicion of neoplastic meningitis (NM) ($n = 41$), and patients with known cancer and suspected NM ($n = 81$) were analyzed separately. Costs incurred by uninformative testing were estimated for CSF cytology, culture, glucose, and protein levels. RESULTS: The positive likelihood ratio (LR+) and negative likelihood ratio (LR-) for CSF cytology were $>10^6$ and 0.33, respectively, in patients without known cancer. Because the prevalence (pretest probability) of NM in this cohort was already very low (0.7%), a negative test decreased the probability of NM to 0.2% (post-test probability). In patients with known cancer, LR+ was 24.3, and LR- was 0.29. A positive test increased the likelihood of NM from 15% to 81%, and a negative test decreased the likelihood of NM to 5%. In patients with known cancer and suspected NM, LR+ was $> 10^6$, and LR- was 0.048. A positive test increased the likelihood of NM from 26% to 100% and a negative test decreased the likelihood to 1.6%. The percentage of performed tests that were uninformative (true negative) was 99%, 80%, and 74% for patients without cancer, patients with cancer without suspected NM, and patients with cancer with suspected NM, respectively. These uninformative tests had a total cost of $110,432. CONCLUSIONS: In patients without known cancer, routine CSF cytology is uninformative, inefficient, and costly. In patients with known cancer but without suspicion of NM, routine CSF cytology is more informative and cost effective. In patients with known cancer and suspected NM, CSF cytology is most informative, and its routine use can be justified.

NO-120. ANAPLASTIC GANGLIOGLIOMAS: REPORT OF 3 CONFIRMED CASES

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Anaplastic gangliogliomas (AGGs) are rare tumors, and published clinical experience with them is limited to case reports and series. Consequently, their clinical and biologic behavior are poorly understood. Here, we present a series of 3 patients with pathology-confirmed AGGs. Patients were identified through the UCSF department of pathology database (1985-2010). AGG patients represented 2.1% of all patients diagnosed with ganglioglioma of all grades during this time. All three patients had a prior diagnosis of low grade ganglioglioma (LGGG); in two cases, histological review revealed regions of hypercellularity and scattered mitoses. A 15-year-old girl received further surgery after LGGG resection because of the above concerns on pathology. She received adjuvant external beam radiation followed by temozolomide. She is currently alive 7 years after diagnosis. A 25-year-old patient who presented with seizures had radiographic progression 1 year after LGGG resection and received gross total resection followed by external beam radiation. He is alive after 10 years. A 40-year-old man presented with intraparenchymal hemorrhage and suffered bilateral ACA infarcts and hydrocephalus. His tumor progressed 8 months after initial resection, upon which time another resection was performed followed by radiation and temozolomide. He died 7 months after diagnosis because of steady neurological decline and seizures. Although the literature commonly shows that AGGs progress from prior LGGGs, it is interesting that in our series, all three patients had prior subtotally resected LGGGs, which raises the possibility that LGGGs may progress to AGGs if not completely resected. Undersampling may have been present as well, which was suggested by higher-grade features seen on pathology review. Our series suggests and underscores the importance of achieving gross total resection to ensure that gangliogliomas are not misdiagnosed AGGs and to potentially prevent progression of LGGGs to AGGs. Patients with AGGs may have favorable long-term survival when managed with aggressive resection followed by adjuvant radiation and/or chemotherapy.